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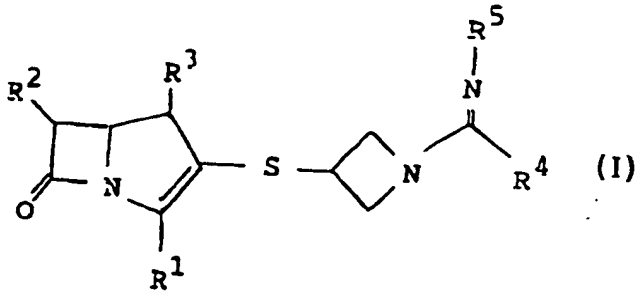
(54) Title: 3-AZETIDINYLTHIO-CARBAPENEME DERIVATIVES, THEIR PREPARATION AND USE AS ANTIMICROBIAL AGENTS



(I)

(57) Abstract

A compound of formula (I) in which R^1 is carboxy, COO^- or protected carboxy, R^2 is hydroxy(lower)alkyl or protected hydroxy(lower)alkyl, R^3 is hydrogen or lower alkyl, and R^4 is substituted lower alkyl or substituted lower alkenyl and R^5 is hydrogen, or R^4 is hydrogen and R^5 is heterocyclic group or lower alkyl or R^4 is hydrogen and the formula: $=N\text{-}R^5$ is N,N-di(lower)alkylimino, or R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group, or pharmaceutically acceptable salts thereof, having antimicrobial activity.

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DESCRIPTION

3-Azetidinylthio-carbapeneme derivatives, their preparation and use as antimicrobial agents

TECHNICAL FIELD

The present invention relates to novel 1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to novel 3-azetidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof, which have antimicrobial activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, to a use of the same as a medicament and to a method for the treatment of infectious diseases in human being or animal.

INDUSTRIAL APPLICABILITY

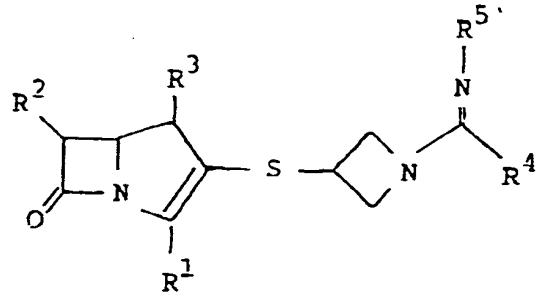
Accordingly, one object of the present invention is to provide novel 3-azetidinylthio-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof, which are highly active against a number of pathogenic microorganisms and are useful as antimicrobial agents.

Another object of the present invention is to provide processes for the preparation of novel 3-azetidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and slats thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said 3-azetidinylthio-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof.

Still further object of the present invention is to provide a use of said 3-azetidinylthio-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof as a medicament, or a method for the treatment of infectious diseases by pathogenic microorganisms in human being or animal.

The object 3-azetidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives are novel and can be represented by the following general formula :



in which R^1 is carboxy, COO^- or protected carboxy,
R^2 is hydroxy(lower)alkyl or protected hydroxy(lower)alkyl,
R^3 is hydrogen or lower alkyl, and
R^4 is substituted lower alkyl or substituted lower alkenyl and R^5 is hydrogen, or
R^4 is hydrogen and R^5 is heterocyclic group or lower alkyl or

R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkylimino, or

R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group,

or pharmaceutically acceptable salts thereof.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include a salt with a base such as an inorganic base salt, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); a salt with an acid such as inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid , glutamic acid, etc.); an intermolecular or intramolecular quaternary salt; and the like.

The said intermolecular quaternary salt can be formed, for example, when R^4 is N-(lower)alkyl-N-carbamoyl(lower)alkylamino (e.g. N-methyl-N-carbamoylmethylamino, etc.), or di(lower)alkylamino (e.g. N,N-dimethylamino, etc.) and said amino is substituted by suitable substituent(s) such as lower alkyl (e.g. methyl, etc.), carbamoyl(lower)alkyl (e.g. carbamoylmethyl, etc.), etc.; and the like.

Suitable intermolecular quaternary salt may include N,N-di(lower)alkyl-N-carbamoylammonio halide (e.g.

N,N-dimethyl-N-carbamoylammonio iodide, N,N-dimethyl-N-carbamoylamino chloride, etc.), and the like.

Said intramolecular quaternary salt can be formed between R^1 and a cation in R^4 and/or R^5, for example, when R^1 is COO^-, and R^4 is hydrogen and the formula : $=N-R^5$ is di(lower)alkyliminio (e.g. dimethyliminio, etc.), or R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group wherein said imino moiety is further substituted by a suitable substituent such as lower alkyl (e.g. methyl, etc.).

In this connection, please note that it may sometime happen said intermolecular quaternary salt and intramolecular quaternary salt can be regarded as substantially the same, in case that said intermolecular quaternary salt can be expressed as corresponding acid addition salt of intramolecular quaternary salt.

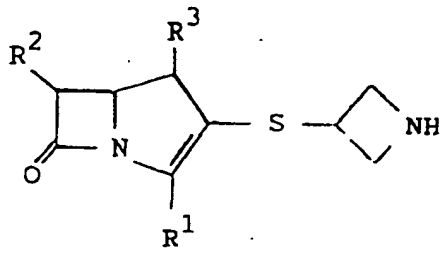
Therefore, in this specification such quaternary salts were expressed by one of these two quaternary salts only for convenient sake.

(continued on the next page)

In the object compound (I) and the intermediary compounds mentioned below, it is to be understood that there may be one or more stereo-isomeric pair(s) such as optical isomers due to asymmetric carbon atom(s), and such isomers are also included within the scope of the present invention.

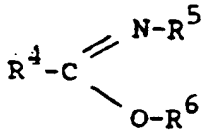
According to the present invention, the object compound (I) or pharmaceutically acceptable salts thereof can be prepared by the processes as illustrated by the following reaction schemes.

Process 1 :



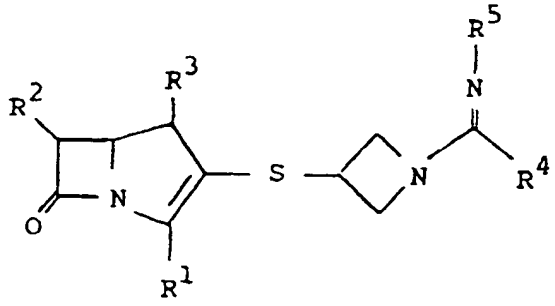
(II)

or salts thereof



(III)

or salts thereof



(I)

or salts thereof

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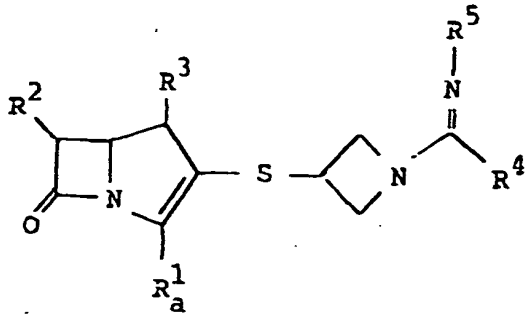
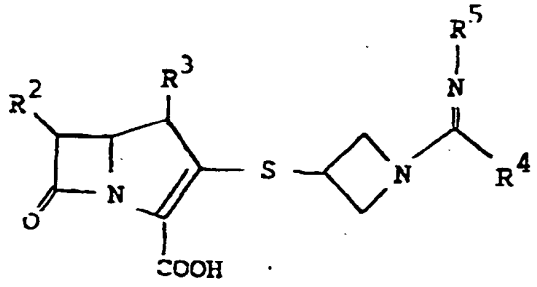
Process 2 :



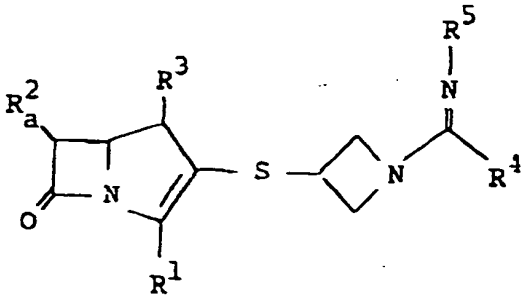
Removal reaction of the carboxy-protective group on R_a^1

(I-a)
or salts thereof



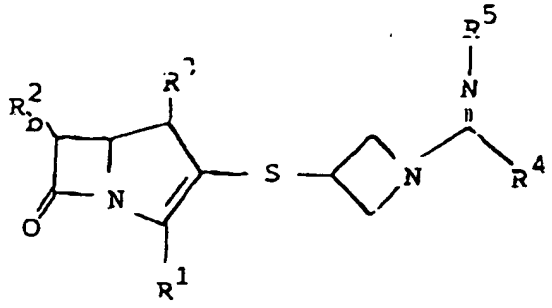
(I-b)
or salts thereof

Process 3 :



Removal reaction of the hydroxy-protective group on R_a^2

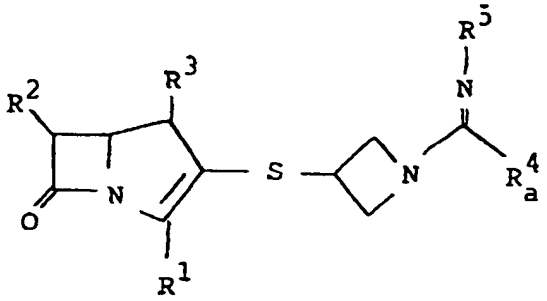
(I-c)
or salts thereof



(I-d)

or salts thereof

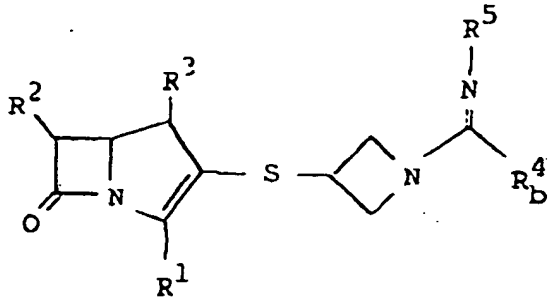
Process 4 :



Removal reaction of the amino- and/or hydroxy-protective group(s) on R_a^4

(I-e)

or salts thereof



(I-f)

or salts thereof

in which R^1, R^2, R^3, and R^4 and R^5 are each as defined above,

$R^1_{a_2}$ is protected carboxy,

R^2_a is protected hydroxy(lower)alkyl,

R^2_b is hydroxy(lower)alkyl,

R^4_a is substituted lower alkyl or substituted lower alkenyl containing protected amino- and/or protected hydroxy-moiety(ies), and R^5 is hydrogen,

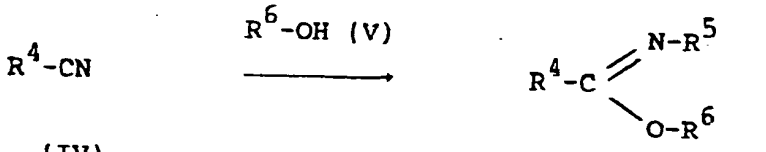
R^4_b is substituted lower alkyl or substituted lower alkenyl containing amino- and/or hydroxy-moiety(ies) and R^5 is hydrogen, and

R^6 is lower alkyl.

The compound (II) used in the Process (I) is disclosed in Japan Kokai No. 255280/88.

The compound (III) used in the Process 1 can be prepared, for example, by the following method or a conventional manner.

Method A



(IV)
or salts thereof

(III)
or salts thereof

in which R^4, R^5 and R^6 are each as defined above.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention

includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s) for alkyl group, and 2 to 4 carbon atom(s) for alkenyl group, unless otherwise indicated.

Suitable "protected carboxy" may include esterified carboxy wherein "esterified carboxy" can be referred to the ones as mentioned below.

Suitable examples of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, hexyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(or 2- or 3- or 4-)-acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)-butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pyvaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)-pentanoyloxyethyl ester, etc.], lower alkanesulfonyl-(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
lower alkoxycarbonyloxy(lower)alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester,

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t-butoxycarbonyloxymethyl ester, 1-(or 2-)-methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, 1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.), phthalidylidene(lower)alkyl ester, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];
lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent(s) such as mono- or di- or triphenyl(lower)alkyl ester which may have halogen or lower alkoxy (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

More preferable example of the protected carboxy thus defined may be C_2-C_4 alkenyloxycarbonyl and phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl.

Suitable "hydroxy(lower)alkyl" may include straight or branched lower alkyl having hydroxy group such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-(hydroxymethyl)ethyl, 1-hydroxy-1-methylethyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, and the like, in which more preferable example may be hydroxy(C_1-C_4)alkyl and the most preferable one may be 1-hydroxyethyl.

Suitable "protected hydroxy(lower)alkyl" means aforementioned hydroxy(lower)alkyl, in which the hydroxy

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group is protected by a conventional hydroxy-protective group such as those mentioned in the explanation of imino-protective group as mentioned below; ar(lower)alkyl such as mono- or di- or triphenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), etc.; trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, diisopropylmethylsilyl, etc.), triarylsilyl (e.g. triphenylsilyl, etc.), triar(lower)alkylsilyl (e.g. tribenzylsilyl, etc.), etc.; and the like.

More preferable example of "protected hydroxy(lower)alkyl thus defined may be [phenyl(or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl, (C_2-C_4)alkenyloxycarbonyloxy(C_1-C_4)alkyl and [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl.

Suitable "lower alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like, in which more preferable example may be C_1-C_4 alkyl and the most preferable one may be methyl for R^3 and ethyl for R^5.

Preferable substituents of "substituted lower alkyl or substituted lower alkenyl" may be

carbamoyl,

N-(or N,N-di)(lower)alkylcarbamoyl,

N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino(lower)-alkyl]carbamoyl,

N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl]carbamoyl,

N-[amino(or protected amino)(lower)alkyl]carbamoyl,

optionally substituted heterocyclicthio,

lower alkylthio,

di(lower)alkylsulfonio,

halo(lower)alkylthio,

lower alkoxy,

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carbamoyloxy,
acylamino,
amino, protected amino,
lower alkylamino, N-protected-N-(lower)alkylamino,
carbamoyl(lower)alkylamino,
N-protected-N-[carbamoyl(lower)alkyl]amino,
N-carbamoyl(lower)alkyl-N-(lower)alkylamino,
N-carbamoyl(lower)alkyl-N,N-di(lower)alkylammonio,
N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)-alkylamino,
N-(lower alkylcarbamoyl)(lower)alkyl-N,N-di(lower)-alkylammonio,
optionally substituted heterocyclic-carbonyl,
optionally substituted
heterocyclic group,
[hydroxy(lower)alkyl]amino,
N-protected-N-[protected hydroxy(lower)alkyl]amino,
N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino,
N,N-di(lower)alkyl-N-[hydroxy(lower)alkyl]ammonio,
N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]amino,
N,N-di(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]ammonio,
N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino, and
N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-ammonio.

Suitable "N-(or N,N-di)(lower)alkylcarbamoyl" means carbamoyl group mono- or disubstituted by above-mentioned lower alkyl such as methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, propylcarbamoyl, dipropylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl and the like, in which more preferable example may be di(C_1-C_4)alkylcarbamoyl,

and the most preferable one may be dimethylcarbamoyl.

Suitable "N-[N-hydroxy(lower)alkyl-N-(lower)-alkylamino(lower)alkyl]carbamoyl" means aforementioned N-(lower)alkylcarbamoyl group, wherein said lower alkyl group is further substituted by N-(lower)alkyl-N-hydroxy(lower)alkylamino group. Said lower alkyl and hydroxy(lower)alkyl moieties are the same ones as mentioned above.

More preferable examples of "N-[N-hydroxy(lower)-alkyl-N-(lower)alkylamino(lower)alkyl]carbamoyl" thus defined may be N-[N-hydroxy(C_1-C_4)alkyl-N-(C_1-C_4)-alkylamino(C_1-C_4)alkyl]carbamoyl, and the most preferable one may be N-[2-[N-(2-hydroxyethyl)-N-methylamino]ethyl]-carbamoyl.

Suitable "N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio(lower)alkyl]carbamoyl" means aforementioned N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino(lower)alkyl]carbamoyl group, wherein said amino group is further substituted by lower alkyl.

More preferable examples of "N-[N-hydroxy(lower)-alkyl-N,N-di(lower)alkylammonio(lower)alkyl]carbamoyl" thus defined may be N-[N-hydroxy(C_1-C_4)alkyl-N,N-di(C_1-C_4)alkylammonio(C_1-C_4)alkyl]carbamoyl, and the most preferable one may be N-[2-[N-(2-hydroxyethyl)-N,N-dimethylammonio]ethyl]carbamoyl.

Suitable "N-[amino(lower)alkyl]carbamoyl" means aforementioned carbamoyl(lower)alkyl group, wherein said lower alkyl group is further substituted by amino, in which more preferable example may be N-[amino(C_1-C_4)alkyl]carbamoyl, and the most preferable one may be 4-aminobutylcarbamoyl.

Suitable "N-[protected amino(lower)alkyl]carbamoyl" means N-[amino(lower)alkyl]carbamoyl group, wherein said amino group is further substituted by suitable amino-protective group such as acyl as mentioned below, in which preferable examples may be N-[lower alkenyloxycarbonylamino(lower)alkyl]carbamoyl, and the most preferable one may be 4-(allyloxycarbonylamino)-butylcarbamoyl.

Suitable optionally substituted heterocyclic moiety of "optionally substituted heterocyclic-thio" may be heterocyclic group as mentioned below, in which preferable examples of said heterocyclic group may be unsaturated 3 to 8-membered, preferably 5 or 6 membered heteromonocyclic group containing 1 to 4 nitrogen atom, optionally substituted by lower alkyl.

Preferable examples of "optionally substituted heterocyclic-thio" thus defined may be lower alkyl-tetrazolylthio, and the most preferable one may be 1-methyltetrazol-5-ylthio.

Suitable "lower alkylthio" means thio group substituted by lower alkyl as mentioned above, in which more preferable example may be (C_1-C_4)alkylthio, and the most preferable one may be methylthio.

Suitable "di(lower)alkylsulfonio" means aforementioned lower alkylthio group, wherein said thio group is further substituted by lower alkyl as mentioned above, in which more preferable example may be di(C_1-C_4)alkylsulfonio, and the most preferable one may be dimethylsulfonio.

Suitable "halo(lower)alkylthio" means aforementioned lower alkylthio, wherein said lower alkyl is further substituted by halogen such as chloro, fluoro, bromo and

iodo, in which more preferable example may be dihalo(C_1-C_4)alkylthio and the most preferable one may be difluoromethylthio.

Suitable "lower alkoxy" may include straight of branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, isopentyloxy, hexyloxy, etc., in which more preferable example may be (C_1-C_4)alkoxy and the most preferable one may be methoxy.

Suitable "acylamino" means amino substituted by acyl group as mentioned below, in which preferable example may be lower alkanoylamino, halo(lower)alkanoylamino, lower alkoxycarbonylamino, lower alkoxy(lower)alkanoylamino, lower alkylsulfonylamino, carbamoylamino, and C_6-C_{10} ar(lower)alkoxycarbonylamino, and the most preferable one may be acetylamino, trifluoroacetylamino, methoxycarbonylamino, mthoxyacetylamino, methylsulfonylamino, carbamoylamino, and benzyloxycarbonylamino.

Suitable "protected amino" may include acylamino as mentioned above, wherein said acyl group can be removed by a conventional method, in which preferable example may be lower alkenyloxycarbonylamino and nitro(C_6-C_{10})ar(lower)alkoxycarbonylamino, and the most preferable one may be allyloxycarbonylamino and p-nitrobenzyloxycarbonylamino.

Suitable "lower alkylamino" means straight or branched lower alkylamino, in which more preferable example may be C_1-C_4 alkylamino, and the most preferable one may be methylamino.

Suitable "N-protected-N-(lower)alkylamino" may

include N-acyl-N-(lower)alkylamino, wherein said acyl group may be the same one as mentioned in protected amino, in which more preferable example may be N-(lower alkenyloxycarbonyl)-N-(lower)alkylamino, and the most preferable one may be N-allyloxycarbonyl-N-methylamino.

Suitable "carbamoyl(lower)alkylamino" means aforementioned lower alkylamino group, wherein said lower alkyl is further substituted by carbamoyl, in which more preferable example may be carbamoyl(C_1-C_4)alkylamino, and the most preferable one may be carbamoylmethylamino.

Suitable "N-protected-N-[carbamoyl(lower)alkyl]amino" means aforementioned carbamoyl(lower)alkylamino group, wherein said amino group is further substituted by amino-protective group such as acyl as mentioned below.

Preferable examples of "N-protected-N-[carbamoyl(lower)alkyl]amino" thus defined may be N-(lower alkenyloxycarbonyl)-N-[carbamoyl(lower)alkyl]amino, and the most preferable one may be N-allyloxycarbonyl-N-(carbamoylmethyl)amino.

Suitable "N-carbamoyl(lower)alkyl-N-(lower)-alkylamino" means aforementioned carbamoyl(lower)alkylamino group, wherein said amino group is further substituted by lower alkyl, in which most preferable example may be N-carbamoylmethyl-N-methylamino.

Suitable "N-carbamoyl(lower)alkyl-N,N-di(lower)alkyl-ammonio" means aforementioned N-carbamoyl(lower)alkyl-N-(lower)alkylamino group, wherein said amino group is further substituted by lower alkyl, in which most preferable example may be N-carbamoylmethyl-N,N-dimethylammonio.

Suitable "N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)alkylamino" means aforementioned N-carbamoyl(lower)alkyl-N-(lower)alkylamino group, wherein said carbamoyl group is further substituted by lower alkyl as mentioned above, in which more preferable example may be N-[(C_1-C_4)alkylcarbamoyl(C_1-C_4)alkyl-N-(C_1-C_4)alkylamino, and the most preferable one may be N-(methylcarbamoyl)methyl-N-methylamino.

Suitable "N-(lower alkylcarbamoyl)(lower)alkyl-N,N-di(lower)alkylammonio" means aforementioned N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)alkylamino group, wherein said amino group is further substituted by lower alkyl as mentioned above, in which more preferable example may be N-[(C_1-C_4)alkylcarbamoyl(C_1-C_4)alkyl-N,N-di(C_1-C_4)-alkylammonio, and the most preferable one may be N-(methylcarbamoyl)methyl-N,N-dimethylammonio.

Suitable optionally substituted heterocyclic moiety of "optionally substituted heterocyclic-carbonyl" may be heterocyclic group as mentioned below, wherein preferable heterocyclic group may be saturated or unsaturated (preferably saturated) 3 to 8-membered, preferably 5 or 6 membered heteromonocyclic group containing 1 to 4 nitrogen atom optionally, substituted by the group consisting of hydroxy, amino(lower)alkanoyl and protected amino(lower)alkanoyl.

Preferable example of "optionally substituted heterocyclic-carbonyl" thus defined may be hydroxyazetidinyl-carbonyl, and piperazinyl-carbonyl substituted by amino(lower)alkanoyl or lower alkenyloxycarbonylamino(lower)alkanoyl, and the most preferable one may be 4-hydroxyazetidin-1-yl-carbonyl, 4-(5-aminopentanoyl)piperazin-1-yl and 4-(5-allyloxycarbonylaminopentanoyl)piperazin-1-yl.

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Suitable "optionally substituted heterocyclic group" may be heterocyclic group as mentioned below, in which more preferable example may be saturated or unsaturated 3 to 8-membered, preferably 5 or 6 membered heteromonocyclic group containing 1 to 4 nitrogen atom, and saturated of unsaturated (preferably unsaturated) 3 to 8-membered, preferably 5 or 6 membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom, optionally substituted by the group consisting of above-mentioned lower alkyl, above-mentioned hydroxy(lower)alkyl and above-mentioned carbamoyl(lower)alkyl.

Preferable examples of "optionally substituted heterocyclic group" thus defined may be saturated or unsaturated 5 or 6 membered heteromonocyclic group containing 1 to 4 nitrogen atom optionally substituted by the group consisting of lower alkyl, hydroxy(lower)alkyl and carbamoyl(lower)alkyl, and unsaturated 5 or 6 membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom, in which more preferable example may be pyridyl, imidazolyl, pyrazolyl, pyrrolidinyl, each of which being optionally substituted by (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl and carbamoyl(C_1-C_4)alkyl, and thiazolyl, and the most preferable example may be 3-pyridyl, 1-methyl-3-pyridinio, 1-carbamoylmethyl-3-pyridinio, 1-pyridinio, 1(or 4)-imidazolyl, 2-methyl-1-imidazolyl, 3-methyl-1-imidazolio, 1,3-dimethyl-2(or 4)-imidazolio, 4-hydroxymethyl-1-methyl-3-imidazolio, 1,2-dimethyl-4-pyrazolio, 1-methyl-1-pyrrolidinio, and 3-thiazolio.

Suitable "[hydroxy(lower)alkyl]amino" means amino group substituted by aforementioned hydroxy(lower)alkyl, in which more preferable example may be hydroxy(C_1-C_4)-alkyl and the most preferable one may be

2-hydroxyethylamino.

Suitable "N-protected-N-[protected hydroxy(lower)-alkyl]amino" means aforementioned hydroxy(lower)alkyl, wherein said hydroxy and amino groups are protected by suitable protective groups such as acyl as mentioned below, in which preferable example may be N-(lower alkenyloxycarbonyl)-N-[lower alkenyloxycarbonyloxy-(lower)alkyl]amino, and the most preferable one may be N-allyloxycarbonyl-N-[2-(allyloxycarbonyloxy)ethyl]amino.

Suitable "N-(lower)alkyl-N-[hydroxy(lower)alkyl]-amino" means aforementioned [hydroxy(lower)alkyl]amino group, wherein said amino group is further substituted by lower alkyl, in which more preferable example may be N-(C_1-C_4)alkyl-N-[hydroxy(C_1-C_4)alkyl]amino, and the most preferable one may be N-methyl-N-(2-hydroxyethyl)amino.

Suitable "N,N-di(lower)alkyl-N-[hydroxy(lower)-alkyl]ammonio" means aforementioned N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino group, wherein said amino group is further substituted by lower alkyl, in which more preferable example may be N,N-di(C_1-C_4)alkyl-N-[hydroxy-(C_1-C_4)alkyl]ammonio, and the most preferable one may be N,N-dimethyl-N-(2-hydroxyethyl)ammonio.

Suitable "N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]amino" means aforementioned N-carbamoyl(lower)alkyl-N-(lower)alkylamino group, wherein said carbamoyl group is further substituted by hydroxy(lower)alkyl as mentioned above, in which most preferable example may be N-methyl-N-[N-(2-hydroxyethyl)-carbamoylmethyl]amino.

Suitable "N-[N-[hydroxy(lower)alkyl]carbamoyl-

(lower)alkyl]-N,N-di(lower)alkylammonio" means aforementioned N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]amino group, wherein said amino group is further substituted by lower alkyl, in which most preferable example may be N-[N-(2-hydroxyethyl)carbamoyl-methyl]-N,N-dimethylammonio.

Suitable "N-(lower)alkyl-N-[carbamoyloxy(lower)-alkyl]amino" means aforementioned "N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino group, wherein said hydroxy group is further substituted by carbamoyl, in which more preferable example may be N-(C_1-C_4)alkyl-N-[carbamoyloxy(C_1-C_4)alkyl]amino, and the most preferable one may be N-methyl-N-[2-(carbamoyloxy)ethyl]amino.

Suitable "N,N-di(lower)alkyl-N-[carbamoyloxy(lower)-alkyl]ammonio" means aforementioned "N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino group, wherein said amino group is further substituted by lower alkyl, in which more preferable example may be N,N-di(C_1-C_4)alkyl-N-[carbamoyloxy(C_1-C_4)alkyl]ammonio, and the most preferable one may be N,N-dimethyl-N-[2-(carbamoyloxy)ethyl]ammonio.

Suitable "aryl" may include C_6-C_{10} aryl such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like, in which most preferable example may be phenyl.

Suitable "acyl" may include aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted with aromatic or heterocyclic group(s) derived from carboxylic, carbonic, sulfonic and carbamic acids.

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl,

hexanoyl, etc.), alkylsulfonyl such as lower alkylsulfonyl (e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)-alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group(s) may include ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

These acyl groups may be further substituted with one or more suitable substituent(s) such as nitro, and the like, and preferable acyl having such substituent(s) may be nitroar(lower)alkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, etc.), and the like.

Suitable "optionally substituted imino-containing heterocyclic group" may be heterocyclic group as mentioned below, wherein said heterocyclic group contains imino moiety, in which preferable example may be unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing an imino moiety, optionally substituted by lower alkyl, more preferable one may be 2H-pyrrolyl, 1-pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, dihydro-triazinyl, each of which being substituted by lower alkyl, and the most preferable one may be 1-methyl-2-pyrrolinio.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, and the like, in which more preferable example may be C_1-C_4 alkylene and the most preferable one may be trimethylene.

Suitable "carbamoyl(lower)alkyl" means aforementioned lower alkyl substituted by carbamoyl, in which most preferable example may be carbamoylmethyl.

Suitable "heterocyclic group" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

More preferable heterocyclic group may be heterocyclic group such as :

-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, 2H-pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperazinyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g.,

tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, 1,3-thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.;

-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

-unsaturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.;

-saturated 3 to 8-membered, preferably 5 or 6-membered heteromonocyclic group containing a sulfur atom, for example, tetrahydrothienyl, etc.;

-unsaturated condensed 7 to 12-membered heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc. and the like;

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wherein said heterocyclic group may be substituted by one or more, preferably one or two suitable substituent(s) such as :

-hydroxy;

-protected hydroxy, in which the hydroxy group is protected by a conventional hydroxy-protective group as mentioned in the explanation of protected hydroxy(lower)alkyl, more preferably tri(C_1-C_4)alkylsilyloxy;

-hydroxy(lower)alkyl or protected hydroxy(lower)alkyl as mentioned above, more preferably hydroxy(C_1-C_4)alkyl (e.g. hydroxymethyl, etc.) or tri(C_1-C_4)alkylsilyloxy-(C_1-C_4)alkyl (e.g. hydroxymethyl, 2-hydroxyethyl, etc.);

-halogen;

-lower alkoxy, which may be straight or branched one alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc., more preferably C_1-C_4 alkoxy;

-lower alkyl as mentioned above, more preferably C_1-C_4 alkyl (e.g. methyl, etc.);

-lower alkoxy(lower)alkyl, in which the lower alkoxy and lower alkyl moieties may respectively be the same as those for lower alkoxy and lower alkyl as mentioned above, more preferably C_1-C_4 alkoxy(C_1-C_4)alkyl;

-lower alkylamino(lower)alkyl, in which the lower alkyl moiety may be the same as those for lower alkyl as mentioned above, more preferably C_1-C_4 alkylamino(C_1-C_4)-alkyl;

-protected lower alkylamino(lower)alkyl, which is the lower alkylamino(lower)alkyl as mentioned above, in which the amino group is protected by a conventional amino-protective group such as acyl as mentioned above, more preferably N-(C_1-C_4)alkyl-N-(C_2-C_4)alkenyloxy-carbonylamino(C_1-C_4)alkyl;

-imino;

-protected imino, in which the imino group is protected by a conventional imino-protective group such as acyl mentioned above, more preferably C_2-C_4 alkenyloxycarbonylimino;

-lower alkylamino, in which the lower alkyl moiety may be the same as those for lower alkyl as mentioned above, more preferably C_1-C_4 alkylamino;

-protected lower alkylamino, which is the lower alkylamino group as mentioned above, in which the amino group is protected by a conventional amino-protective group such as acyl mentioned above, more preferably C_1-C_4 alkylamino;

-mono(or di)(lower)alkylcarbamoyloxy, in which the lower alkyl moiety may be the same as those for lower alkyl as mentioned above, more preferably mono(or di)(C_1-C_4)alkylcarbamoyloxy;

-carbamoyl(lower)alkyl as mentioned above (e.g. carbamoylmethyl, etc.);

-amino(lower)alkanoyl such as aminoacetyl, aminopropionyl, aminobutyryl, aminoisobutyryl, aminovaleryl, aminoisovaleryl, aminohexanoyl, and the like (e.g. 5-aminovaleryl, etc.);

-protected amino(lower)alkanoyl, wherein said amino(lower)alkanoyl group and amino protective group may be the same as mentioned above, in which preferable example may be lower alkenyloxycarbonylamino(lower)-alkanoyl [e.g. 5-(allyloxycarbonylamino)valeryl, etc.]; and the like.

Preferred embodiments of R^1, R^2, R^3, R^4 and R^5 are as follows.

R^1 is carboxy or esterified carboxy,

R^2 is hydroxy(lower)alkyl, acyloxy(lower)alkyl, mono-(or di or tri)phenyl(lower)alkoxy(lower)alkyl,

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tri(lower)alkylsilyloxy(lower)alkyl, triphenylsilyloxy(lower)alkyl or tribenzylsilyloxy(lower)alkyl,

R^3 is hydrogen or lower alkyl,

R^4 is carbamoyl(lower)alkyl; lower alkylthio(lower)alkyl; amino(lower)alkyl; mono(or di)(lower)alkylamino-(lower)alkyl; lower alkoxy(lower)alkyl; acylamino(lower)alkyl; mono(or di)(lower)alkyl-carbamoyl(lower)alkyl; N-(lower)alkyl-N-carbamoyl(lower)alkylamino(lower)-alkyl, pyrrolylthio(lower)alkyl, pyrrolinylthio-(lower)alkyl, imidazolylthio(lower)alkyl, pyrazolylthio(lower)alkyl, pyridylthio(lower)alkyl, and its N-oxide, pyrimidylthio(lower)alkyl, pyrazinylthio(lower)alkyl, pyridazinylthio(lower)-alkyl, triazolylthio(lower)alkyl, tetrazolylthio-(lower)alkyl, dihydrotriazinylthio(lower)alkyl, each of said heterocyclic group is optionally substituted by lower alkyl; azetidinylcarbonyl(lower)alkyl, pyrrolidinyl-carbonyl(lower)alkyl, imidazolidinylcarbonyl(lower)-alkyl, piperidinylcarbonyl(lower)alkyl, pirazolidinylcarbonyl(lower)alkyl, piperazinylcarbonyl(lower)alkyl, each of said heterocyclic group is optionally substituted by hydroxy; and

R^5 is hydrogen, or

R^1 is carboxy, COO^- or esterified carboxy,

R^2 is hydroxy(lower)alkyl, aryloxy(lower)alkyl, mono(or di or tri)phenyl(lower)alkoxy(lower)alkyl, tri(lower)alkylsilyloxy(lower)alkyl, triphenylsilyloxy(lower)alkyl or tribenzylsilyloxy(lower)alkyl,

R^3 is hydrogen or lower alkyl,

R^4 is carbamoyl(lower)alkyl,
N-(or N,N-di)(lower)alkylcarbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino-(lower)alkyl]carbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl]carbamoyl(lower)alkyl,
N-[amino(or protected amino)(lower)alkyl]-carbamoyl(lower)alkyl,
heterocyclic-thio(lower)alkyl optionally substituted by lower alkyl, lower alkylthio(lower)alkyl, di(lower)alkylsulfonio(lower)alkyl, halo(lower)alkylthio(lower)alkyl,
lower alkoxy(lower)alkyl, carbamoyloxy(lower)alkyl, acylamino(lower)alkyl, amino(or protected amino)-(lower)alkyl, lower alkylamino(lower)alkyl, N-protected-N-(lower)alkylamino(lower)alkyl, [carbamoyl(lower)alkylamino](lower)alkyl, N-protected-N-[carbamoyl(lower)alkyl]amino(lower)-alkyl, N-carbamoyl(lower)alkyl-N-(lower)alkylamino-(lower)alkyl, N-carbamoyl(lower)alkyl-N,N-di(lower)-alkylammonio(lower)alkyl, N-(lower alkylcarbamoyl)-(lower)alkyl-N-(lower)alkylamino(lower)alkyl, N-(lower alkylcarbamoyl)(lower)alkyl-N,N-di(lower)-alkylammonio(lower)alkyl,
heterocyclic-carbonyl(lower)alkyl optionally substituted by the group consisting of hydroxy and amino(or protected amino)(lower)alkanoyl,
heterocyclic(lower)alkyl optionally substituted by the group consisting of lower alkyl and hydroxy(lower)alkyl, heterocyclic(lower)alkenyl optionally substituted by the group consisting of lower alkyl and carbamoyl(lower)alkyl,
[hydroxy(lower)alkyl]amino(lower)alkyl,
N-protected-N-[protected hydroxy(lower)alkyl]amino-(lower)alkyl, N-(lower)alkyl-N-[hydroxy(lower)-

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alkyl]amino(lower)alkyl,
N,N-di(lower)alkyl-N-[hydroxy(lower)alkyl]ammonio-(lower)alkyl, N-(lower)alkyl-N-[N-[hydroxy(lower)-alkyl]carbamoyl(lower)alkyl]amino(lower)alkyl,
N,N-di(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]ammonio(lower)alkyl,
N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino-(lower)alkyl, or
N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-ammonio(lower)alkyl, and R^5 is hydrogen, or

R^4 is hydrogen and R^5 is heterocyclic group or lower alkyl, or

R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkyliminio, or

R^4 and R^5 are combined together to form optionally substituted N-containing heterocyclic group.

More preferred embodiments of R^1, R^2, R^3, R^4 and R^5 are as follows.

R^1 is carboxy,
R^2 is hydroxy(lower)alkyl,
R^3 is lower alkyl,
R^4 is carbamoyl(lower)alkyl, lower alkylthio(lower)alkyl, di(lower)alkylamino(lower)alkyl, lower alkoxy(lower)alkyl, lower alkanoylamino(lower)alkyl, di(lower)alkylcarbamoyl(lower)alkyl, N-(lower)alkyl-N-carbamoyl(lower)alkylamino(lower)-alkyl, tetrazolylthio(lower)alkyl optionally substituted by lower alkyl, azetidinylcarbonyl(lower)alkyl optionally substituted by hydroxy, and
R^5 is hydrogen, or

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R^1 is carboxy or COO^-,
R^2 is hydroxy(lower)alkyl (e.g. 1-hydroxyethyl, etc.),
R^3 is lower alkyl (e.g. methyl, etc.),
R^4 is carbamoyl(lower)alkyl (e.g. carbamoylmethyl, etc.),
N-(or N,N-di)(lower)alkylcarbamoyl(lower)alkyl (e.g. N,N-dimethylcarbamoylmethyl, etc.),
N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino(lower)-alkyl]carbamoyl(lower)alkyl [e.g. [N-[2-[N-(2-hydroxyethyl)-N-methylamino]ethyl]-carbamoyl]methyl, etc.], N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio(lower)alkyl]carbamoyl-(lower)alkyl [e.g. [N-[2-[N-(2-hydroxyethyl)-N,N-dimethylammonio]ethyl]carbamoyl]methyl, etc.],
N-[amino(or lower alkenyloxycarbonylamino)(lower)-alkyl]carbamoyl(lower)alkyl [e.g. N-(4-aminobutyl)carbamoylmethyl, N-(4-allyoxycarbonylaminobutyl)carbamoylmethyl, etc.], lower alkyltetrazolylthio(lower)alkyl [e.g. (1-methyltetrazol-5-ylthio)methyl, etc.),
lower alkylthio(lower)alkyl (e.g. methylthiomethyl, etc.), di(lower)alkylsulfonio(lower)alkyl (e.g. dimethylsulfoniomethyl, etc.),
halo(lower)alkylthio(lower)alkyl (e.g. difluoromethylthiomethyl, etc.),
lower alkoxy(lower)alkyl (e.g. methoxymethyl, etc.),
carbamoyloxy(lower)alkyl (e.g. carbamoyloxymethyl, etc.), lower alkanoylamino(lower)alkyl (e.g. acetylaminomethyl, etc.),
halo(lower)alkanoylamino(lower)alkyl (e.g trifluoroacetylaminomethyl, etc.),
lower alkoxycarbonylamino(lower)alkyl (e.g. methoxycarbonylaminomethyl, etc.),
lower alkoxy(lower)alkanoylamino(lower)alkyl (e.g. methoxyacetylaminomethyl, etc.),
lower alkylsulfonylamino(lower)alkyl (e.g.

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methylsulfonylaminomethyl, etc.),
carbamoylamino(lower)alkyl (e.g. carbamoylaminomethyl, etc.),
phenyl(lower)alkoxycarbonylamino(lower)alkyl [e.g. 2-(benzyloxycarbonylamino)ethyl, etc.],
amino[or lower alkenyloxycarbonylamino or nitro(C_6-C_{10})ar(lower)alkoxycarbonylamino]-(lower)alkyl [e.g. aminomethyl, 2-aminoethyl, allyloxycarbonylaminomethyl, 2-(p-nitrobenzyloxy-carbonylamino)ethyl, etc.], lower alkylamino(lower)alkyl or N-(lower)alkenyloxy-carbonyl-N-(lower)alkylamino(lower)alkyl [e.g. methylaminomethyl, (N-allyloxycarbonyl-N-methylamino)methyl, etc.],
[carbamoyl(lower)alkylamino](lower)alkyl or N-(lower)alkenyloxycarbonyl-N-[carbamoyl(lower)-alkyl]amino(lower)alkyl [e.g. (carbamoylmethylamino)methyl, 2-(carbamoylmethylamino)ethyl, [N-allyloxycarbonyl-N-(carbamoylmethyl)amino]methyl, 2-[N-allyloxycarbonyl-N-(carbamoylmethyl)-amino]ethyl, etc.],
N-carbamoyl(lower)alkyl-N-(lower)alkylamino(lower)-alkyl [e.g. 2-(N-carbamoylmethyl-N-methylamino)ethyl, etc.],
N-carbamoyl(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl [e.g. 3-(N-carbamoylmethyl-N,N-dimethylammonio)propyl, etc.],
N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)alkyl-amino(lower)alkyl [e.g. 3-[N-(methylcarbamoyl)-methyl-N-methylamino]propyl, etc.],
N-(lower alkylcarbamoyl)(lower)alkyl-N,N-di(lower)-alkylammonio(lower)alkyl [e.g. 3-[N-(methylcarbamoyl)methyl-N,N-dimethylammonio]-propyl, etc.],

hydroxyazetidinylcarbonyl(lower)alkyl (e.g. 4-hydroxyazetidin-1-ylcarbonylmethyl, etc.), amino(or lower alkenyloxycarbonylamino)(lower)-alkanoylpiperazinylcarbonyl(lower)alkyl [e.g. [4-(5-aminopentanoyl)piperazin-1-yl]carbonylmethyl, [4-(5-allyloxycarbonylaminopentanoyl)piperazin-1-yl]carbonylmethyl, etc.], pyridyl(lower)alkyl [e.g. 3-pyridylmethyl, 2-(3-pyridyl)ethyl, 3-(1-pyridinio)propyl, etc.], lower alkylpyridyl(lower)alkyl [e.g. (1-methyl-3-pyridinio)methyl, 2-(1-methyl-3-pyridinio)ethyl, etc.], imidazolyl(lower)alkyl [e.g. 3-(1-imidazolyl)propyl, 4-imidazolylmethyl, 2-(4-imidazolyl)ethyl, etc.], lower alkylimidazolyl(lower)alkyl [e.g. 3-(2-methylimidazol-1-yl)propyl, (3-methyl-1-imidazolio)methyl, 3-(3-methyl-1-imidazolio)propyl, 5-(3-methyl-1-imidazolio)pentyl, 1,3-dimethyl-2(or 4)-imidazoliomethyl, etc.], hydroxy(lower)alkylimidazolyl(lower)alkyl [e.g. 3-[3-(2-hydroxyethyl)-1-imidazolio]propyl, etc.], hydroxy(lower)alkylimidazolyl(lower)alkyl substituted by lower alkyl [e.g. 3-(4-hydroxymethyl-1-methyl-3-imidazolio)propyl, etc.], thiazolyl(lower)alkyl [e.g. 3-(3-thiazolio)propyl, etc.], pyrazolyl(lower)alkyl [e.g. (1,2-dimethyl-4-pyrazolio)methyl, etc.], pyrrolidinyl(lower)alkyl [e.g. 3-(1-pyrrolidinyl)propyl, etc.], lower alkylpyrrolidinyl(lower)alkyl [e.g. 3-(1-methyl-1-pyrrolidinio)propyl, etc.], pyridyl(lower)alkenyl [e.g. 2-(3-pyridyl)ethenyl, etc.], lower alkylpyridyl(lower)alkenyl [e.g. 2-(1-methyl-3-pyridinio)ethenyl, etc.],

carbamoyl(lower)alkylpyridyl(lower)alkyl [e.g. 2-(1-carbamoylmethyl-3-pyridinio)ethenyl, etc.], lower alkylimidazolyl(lower)alkenyl [e.g. 2-(1,3-dimethyl-2-imidazolio)ethenyl, etc.], [hydroxy(lower)alkyl]amino(lower)alkyl [e.g. (2-hydroxyethylamino)methyl, 2-(2-hydroxyethylamino)ethyl, etc.], N-(lower)alkenyloxycarbonyl-N-[lower alkenyloxycarbonyloxy(lower)alkyl]amino(lower)alkyl [e.g. [N-allyloxycarbonyl-N-[2-(allyloxycarbonyloxy)-ethyl]amino]methyl, etc.], N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino(lower)-alkyl [e.g. 2-[N-methyl-N-(2-hydroxyethyl)amino]-ethyl, 3-[N-methyl-N-(2-hydroxyethyl)amino]-propyl, etc.], N,N-di(lower)alkyl-N-[hydroxy-(lower)alkyl]ammonio(lower)alkyl [e.g. 3-[N,N-dimethyl-N-(2-hydroxyethyl)ammonio]propyl, etc.], N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]amino(lower)alkyl [e.g 3-[N-methyl-N-[N-(2-hydroxyethyl)carbamoylmethyl]-amino]propyl, etc.], N-[N-[hydroxy(lower)alkyl]carbamoyl(lower)alkyl]-N,N-di(lower)alkylammonio(lower)alkyl [e.g 3-[N-methyl-N-[N-(2-hydroxyethyl)carbamoylmethyl]-ammonio]propyl, etc.], N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino-(lower)alkyl [e.g. 3-[N-methyl-N-[2-(carbamoyloxy)-ethyl]amino]propyl, etc.], or N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-ammonio(lower)alkyl [e.g. 3-[N,N-dimethyl-N-[2-(carbamoyloxy)ethyl]ammonio]propyl, etc.], and R^5 is hydrogen, or

R^4 is hydrogen and R^5 is thiadiazolyl (e.g. 1,3,4-thiadiazol-5-yl, etc.) or lower alkyl (e.g. methyl, etc.), or

R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)-alkyliminio (e.g. N,N-dimethyliminio, etc.), or

R^4 and R^5 are combined together to form 1-pyrrolinyl ring optionally substituted by lower alkyl (e.g. 1-methyl-2-pyrrolinio ring, etc.).

The processes for the preparation of the object compound (I) of the present invention are explained in detail in the following.

(1) Process 1 :

The compound (I) or salts thereof can be prepared by reacting the compound (II) or salts thereof with the compound (III) or salts thereof.

Suitable salts of the compound (II) may be the same as those for the compound (I).

Suitable salts of the compound (III) may be the same acid addition salts and/or intermolecular quaternary salt as exemplified for the compound (I).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane, water, methanol, ethanol, buffer solution (e.g. phosphate buffer, etc.), etc., or a mixture thereof.

This reaction can be carried out in the presence of an organic or inorganic base such as those given in the explanation of Process 2.

The reaction temperature is not critical, and the reaction is usually carried out under from cooling to warming.

(2) Process 2 :

The compound (I-b) or salts thereof can be prepared by subjecting the compound (I-a) or salts thereof to removal reaction of the carboxy-protective group on R_a^1.

Suitable salts of the compounds (I-a) and (I-b) may be the same as those for the compound (I).

The present reaction is usually carried out by a conventional method such as hydrolysis, reduction, and the like.

(i) Hydrolysis :

Hydorlysis is preferably carried out in the presence of a base or an acid. Suitable base may include an alkalimetal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), an alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), and alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), and the like.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc.). The acidic hydrolysis using trifluoroacetic acid is usually accelerated by addition of cation trapping agent (e.g. phenol, anisole, etc.).

In case that the hydroxy-protective group is tri(lower)alkylsilyl, the hydrolysis can be carried out in the presence of tri(lower)alkylammonium halide (e.g. tributylammonium fluoride, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence

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the reaction such as water, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, dioxane, acetone, etc., or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

(ii) Reduction :

The reduction method applicable for this removal reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, sulfuric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, palladium hydroxide on carbon, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), and the like.

In case that the catalytic reduction is applied, the reaction is preferably carried out around neutral condition.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, acetate buffer, etc.), and the like, or a mixture thereof.

The reaction temperature is not critical and the

reaction is usually carried out under from cooling to warming.

In case that the carboxy-protective group is allyl group, it can be deprotected by hydrogenolysis using a palladium compound.

Suitable palladium compound used in this reaction may be palladium on carbon, palladium hydroxide on carbon, palladium chloride, a palladium-ligand complex such as tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), di[1,2-bis(diphenylphosphino)ethane]palladium(0), tetrakis(triphenyl phosphite)palladium(0), tetrakis(triethyl phosphite)palladium(0), and the like.

The reaction can preferably be carried out in the presence of a scavenger of allyl group generated in situ, such as amine (e.g. morpholine, N-methylaniline, etc.), an activated methylene compound (e.g. dimedone, benzoylacetate, 2-methyl-3-oxovaleric acid, etc.), a cyanohydrin compound (e.g. α-tetrahydropyranyloxybenzyl-cyanide, etc.), alkanoic acid or a salt thereof (e.g. formic acid, acetic acid, ammonium formate, sodium acetate, sodium 2-ethylhexanoate, etc.), N-hydroxysuccinimide, and the like.

This reaction can be carried out in the presence of a base such as lower alkylamine (e.g. butylamine, triethylamine, etc.), pyridine, and the like.

When palladium-ligand complex is used in this reaction, the reaction can preferably be carried out in the presence of the corresponding ligand (e.g. triphenylphosphine, triphenyl phosphite, triethyl phosphite, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, dioxane, tetrahydrofuran, acetonitrile, chloroform,

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dichloromethane, dichloroethane, ethyl acetate, etc., or a mixture thereof.

The removal reaction can be selected according to the kind of carboxy-protective group to be removed.

(3) Process 3 :

The compound (I-d) or salts thereof can be prepared by subjecting the compound (I-c) or salts thereof to removal reaction of the hydroxy-protective group on R_a^2.

Suitable salts of the compounds (I-c) and (I-d) may be the same as those for the compound (I).

This reaction is usually carried out by a conventional method such as hydrolysis, reduction, and the like.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, solvent, etc.) are substantially the same as those illustrated for removal reaction of the carboxy-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

In case that the hydroxy-protective group is tri(lower)alkylsilyl, the removal of this protective group can also be carried out in the presence of tetra(lower)alkylammonium fluoride (e.g. tetrabutylammonium fluoride, etc.).

(4) Process 4 :

The compound (I-f) or salts thereof can be prepared by subjecting the compound (I-e) or salts thereof to removal reaction of the amino- and/or hydroxy-protective group on R_a^4.

Suitable salts of the compounds (I-e) and (I-f) may be the same as those for the compound (I).

This reaction is usually carried out by a conventional method such as hydrolysis, reduction, and the like.

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The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, solvent, etc.) are substantially the same as those illustrated for removal reaction of the carboxy-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

In case that the hydroxy-protective group is tri(lower)alkylsilyl, the removal of this protective group can also be carried out in the presence of tetra(lower)alkylammonium fluoride (e.g. tetrabutylammonium fluoride, etc.).

The object compounds obtained according to the Processes, can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

Method A for preparing the compound (III) or salts thereof is explained in detail in the following.

(A) Method A

The compound (III) or salts thereof can be prepared by reacting the compound (IV) with the compound (V).

Suitable salts of the compound (IV) may be the same as those for the compound (III).

The starting compound (IV) can be prepared by a conventional process.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, allyl alcohol, etc.), pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

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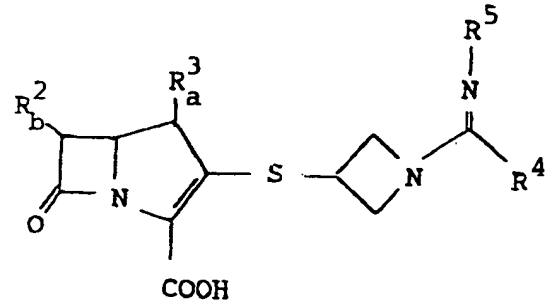
The object compound (I) and pharmaceutically acceptable salts thereof of the present invention are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents.

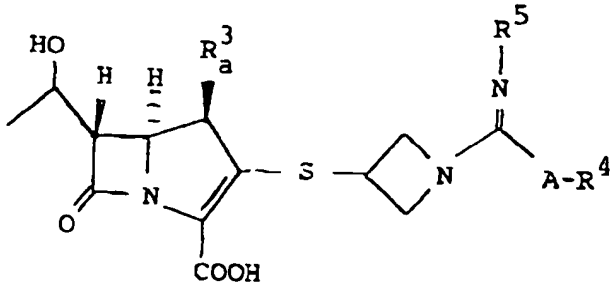
In the present invention, the object compound (I) possessing more potent antimicrobial activity can be represented by the following formula :



(I')

in which R^2_b, R^4 and R^5 are each as defined above, and R^3_a is lower alkyl,
and pharmaceutically acceptable salts thereof.

Particularly, the compound (I) possessing the most potent antimicrobial activity can be represented by the following formula :



in which R^3_a, R^4 and R^5 are each as defined above, and pharmaceutically acceptable salts thereof.

In addition, quaternary salts of the compound (I) having di(lower)alkylamino or N-(lower)alkyl-N-carbamoyl-(lower)alkylamino as R^4 show fairly low toxicity.

Now in order to show the utility of the object compound (I), the test data on antimicrobial activity of the representative compound of the compound (I) of this invention is shown in the following.

in vitro Antimicrobial Activity

Test Method

in vitro Antimicrobial Activity was determined by the two-fold agar-plate dilution method as described blow.

One loopful of an overnight culture of a test strain in Trypticase-soy broth (10^6 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of the test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 37°C for 20 hours.

Test compound :

The product of Example 3.

Test Result :

Test Strain	MIC (μg/ml)
S. aureus 2538	0.78

For therapeutic administration, the object compound

(I) and the pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound, as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade, and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, tartaric acid, citric acid, fumaric acid, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general, amount between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg, of the object compound (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating this invention in more detail.

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Preparation 1

Ethanol (280 ml) was added to acetyl chloride (148 ml) at 0°C in a dry nitrogen atmosphere. After stirring for 10 minutes at 0°C, the mixture was added to cyanoacetamide (50 g). The mixture was stirred at 0°C for 5 hours and allowed to stand at 0°C for 18 hours. The mixture was added to isopropyl ether (420 ml). The resultant crystal was filtrated and washed with a mixture of isopropyl ether and ethanol (3:2). The crystal was dried under reduced pressure for 5 hours to give ethyl carbamoylacetimidate hydrochloride (81.8 g).

NMR (DMSO-d_6, δ) : 1.36 (3H, t, J=6.0Hz), 3.71 (3H, s), 4.47 (2H, q, J=7.5Hz)

Preparation 2-1)

To a stirred solution of chloroacetonitrile (3 ml) and 1-methyl-5-mercaptotetrazole (5.50 g) in dichloromethane (30 ml) was added triethylamine (13 ml) at 0°C. After stirring at 0°C for 1 hour, the reaction mixture was diluted with ethyl acetate (100 ml) and the resulting precipitate was filtrated off. The filtrate was washed in turn with brine, hydrochloric acid (6N), aqueous potassium carbonate (30%) and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 5-cyanomethylthio-1-methyltetrazole (5.66 g).

NMR ($CDCl_3$, δ) : 4.01 (3H, s), 4.17 (2H, s)

Preparation 2-2)

Ethyl (1-methyltetrazol-5-ylthio)acetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7Hz), 4.00 (3H, s), 4.46 (2H, q, J=7Hz), 4.47 (2H, s)

Preparation 3

Ethyl methylthioacetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.41 (3H, t, J=7Hz), 2.26 (3H, s), 3.73 (2H, s), 4.52 (2H, q, J=7Hz)

Preparation 4

Ethyl methoxyacetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

IR (Nujol) : 1660 cm^{-1}

Preparation 5-1)

To a stirred solution of aminoacetonitrile hydrochloride (25.0 g) in a mixture of water (200 ml) and tetrahydrofuran (300 ml) was added acetyl chloride (39 ml) at 0°C while adjusting pH to around 9.5 with aqueous sodium hydroxide (4N). After evaporation of the solvent, the residue was extracted with ethyl acetate (1 ℓ x 2). The combined extract was evaporated in vacuo to give (acetylamino)acetonitrile (25.78 g).

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 4.10 (2H, d, J=5.2Hz), 8.57 (1H, br s)

Preparation 5-2)

Ethyl (2-carbamoyloxyethylthio)acetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.39 (3H, t, J=7Hz), 2.89 (2H, t, J=6Hz), 3.78 (2H, s), 4.06 (2H, t, J=6Hz), 4.48 (2H, q, J=7Hz)

Preparation 6-1)

To a solution of dimethylamine hydrochloride (27 g) and triethylamine (46 ml) in methanol (100 ml) was added methyl cyanoacetate (26.5 ml). After 3 days, the solvent

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was removed and the residue was dissolved in ethyl acetate. Precipitate was filtered off and the filtrate was concentrated in vacuo. The residual oil was chromatographed on silica gel, eluting with a mixture of hexane and ethyl acetate (1:2 to 0:1, V/V) to give dimethylcarbamoylacetonitrile (21.9 g).

NMR (DMSO-d_6, δ) : 2.84 (3H, s), 2.92 (3H, s), 3.99 (2H, s)

Preparation 6-2)

To a solution of dimethylcarbamoylacetonitrile (15.0 g) in a mixture of ethanol (7.85 ml) and chloroform (10 ml) was introduced hydrogen chloride (4.88 g) at 0°C. The resultant mixture was allowed to stand at 0°C for 24 hours. The precipitates were collected by filtration, washed with diethyl ether and dried in vacuo to give ethyl dimethylcarbamoylacetimidate hydrochloride (27.10 g).

NMR (DMSO-d_6, δ) : 1.36 (3H, t, J=7Hz), 2.86 (3H, s), 3.00 (3H, s), 4.01 (2H, s), 4.50 (2H, q, J=7Hz), 12.0 (1H, br s)

Preparation 7-1)

A mixture of 1-(diphenylmethyl)-3-hydroxyazetidine hydrochloride (43.7 g) and 10% palladium on carbon (50% wet, 8.74 g) in methanol (880 ml) was stirred for 10 hours under hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in water and washed with ethyl acetate. Evaporation of the solvent gave 3-hydroxyazetidine hydrochloride (17.9 g).

NMR (DMSO-d_6, δ) : 3.71-3.80 (2H, m), 3.98-4.07 (2H, m), 4.47-4.61 (1H, m)

Preparation 7-2)

To a solution of 3-hydroxyazetidine hydrochloride (17.3 g) and triethylamine (26 ml) in methanol (65 ml) was added methyl cyanoacetate (12.7 ml). After 7 days, the solvent was removed and the residue was dissolved in ethyl acetate. Resultant precipitate was filtered off and the filtrate was concentrated in vacuo to give 3-(3-hydroxyazetidin-1-yl)-3-oxopropiononitrile (18.2 g).

NMR (DMSO-d_6, δ) : 3.57-3.64 (1H, m), 3.84-3.91 (1H, m), 4.02-4.11 (1H, m), 4.24-4.32 (1H, m), 4.38-4.47 (1H, m), 5.50 (2H, d, J=6Hz)

Preparation 7-3)

To a solution of 2-(3-hydroxyazetidin-1-yl)-2-oxopropiononitrile (15 g) in a mixture of ethanol (6.9 ml) and chloroform (45 ml) was added hydrogen chloride gas with stirring at 0°C. Resultant white precipitate was filtered off, washed with diisopropyl ether, and dried in vacuo to give ethyl 3-(3-hydroxyazetidin-1-yl)-3-oxopropionimidate hydrochloride (13.7 g).

NMR (DMSO-d_6, δ) : 1.41 (3H, t, J=6Hz), 3.56-4.55 (9H, m)

Preparation 8-1)

To a suspension of N,N-dimethylglycineamide (2.20 g) in 2-butanone (10 ml) was added 4-bromobutyronitrile (2.15 ml) and the resulting mixture was heated to 80°C for 4 hours. The resulting precipitate was collected by filtration, washed with 2-butanone, and dried in vacuo to give N-carbamoylmethyl-N-(3-cyanopropyl)-N,N-dimethylammonium bromide (3.55 g).

NMR (DMSO-d_6, δ) : 1.97-2.14 (2H, m), 2.65 (2H, t, J=7.2Hz), 3.22 (6H, s), 3.53-3.63 (2H, m), 4.12 (2H, s), 7.27 (1H, br s), 7.98 (1H, br s)

Preparation 8-2)

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Ethyl 4-(N-carbamoylmethyl-N,N-dimethylammonio)-butyrimidate bromide hydrochloride was obtained from N-carbamoylmethyl-N-(3-cyanopropyl)-N,N-dimethylammonium bromide (3.54 g) in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.38 (3H, t, J=7.0Hz), 1.90-2.22 (2H, m), 2.68 (2H, t, J=7.0Hz), 3.21 (6H, s), 3.35-3.62 (2H, m), 4.10 (2H, s), 4.40 (2H, q, J=7.0Hz), 7.73 (1H, br s), 8.05 (1H, br s)

Preparation 9-1)

To a suspension of sodium hydride (6.8 g, 62% oil) in tetrahydrofuran (200 ml) was heated to 40°C under nitrogen atmosphere, and then, to this solution was added dropwise allyloxycarbonylaminoacetonitrile (22.3 g). After 20 minutes, to the reaction mixture was added dropwise ethyl bromoacetate (18.5 ml). After 4 hours, the reaction mixture was cooled to room temperature and water was added thereto (5 ml). The solution was poured into a mixture of ethyl acetate (1 ℓ) and water, and separated organic layer was washed three times with brine and then dried over magnesium sulfate. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (400 ml) eluting in turn with n-hexane, 10% ethyl acetate in n-hexane and 33% n-hexane in ethyl acetate. The fractions containing desired compound were concentrated in vacuo to give ethyl 2-[N-(allyloxycarbonyl)-N-(cyanomethyl)amino]-acetate (30.96 g).

NMR ($CDCl_3$, δ) : 1.30 (3H, t, J=7.16Hz), 4.15 (2H, d, J=6.78Hz), 4.23 (2H, q, J=7.14Hz), 4.36 (2H, d, J=11.07Hz), 4.60-4.70 (2H, m), 5.20-5.41 (2H, m), 5.75-6.02 (1H, m)

Preparation 9-2)

To a solution of ethyl 2-[N-(allyloxycarbonyl)-N-

(cyanomethyl)amino]acetate (15 g) in ethanol (80 ml) was added ammonia solution (28% in water) (60 ml) at room temperature, and the mixture was allowed to stand for 1 day. Solvent was removed under reduced pressure to give a residue, which was chromatographed on silica gel (200 ml) eluting in turn with 33% n-hexane in ethyl acetate and ethyl acetate to give N-(allyloxycarbonyl)-N-(carbamoylmethyl)aminoacetonitrile (10.85 g).

NMR ($CDCl_3$, δ) : 4.08 (2H, s), 4.37 (2H, s), 4.60-4.70 (2H, m), 5.20-5.40 (2H, m), 5.92 (1H, br s), 6.20 (2H, br s)

Preparation 9-3)

Ethyl 2-[N-(allyloxycarbonyl)-N-(carbamoylmethyl)-amino]acetimidate hydrochloride was obtained in 92% yield in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=6.56Hz), 4.00-4.15 (2H, m), 4.40-4.60 (4H, m), 5.15-5.35 (2H, m), 5.58 (2H, br s), 5.80-5.92 (1H, m)

Preparation 10-1)

A suspension of sodium hydride (3.54 g, 62% oil) in tetrahydrofuran (150 ml) was heated to 40°C under nitrogen atmosphere, and then to this solution was added dropwise N-(allyloxycarbonyl)aminoacetonitrile (11.7 g). After 20 minutes, to the reaction mixture was added dropwise 2-tert-butyldimethylsilyloxy-1-iodoethane (25 g), and then the mixture was refluxed for an additional 6 hours. The reaction mixture was cooled to room temperature, which was poured into a mixture of ethyl acetate (500 ml) and water (100 ml). The organic layer was separated, washed in turn with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (300 ml) eluting in turn

with 10%, 25%, 33% ethyl acetate in hexane to give N-(allyloxycarbonyl)-N-(2-tert-butyldimethylsilyloxyethyl)aminoacetonitrile (10.4 g).

NMR ($CDCl_3$, δ) : 0.08 (6H, s), 0.90 (9H, s), 3.51 (2H, t, J=5.0Hz), 3.79 (2H, m), 4.28-4.34 (2H, m), 4.50-4.60 (2H, m), 5.10-5.40 (2H, m), 5.70-6.05 (1H, m)

Preparation 10-2)

A mixture of N-(allyloxycarbonyl)-N-(2-t-butyldimethylsilyloxyethyl)aminoacetonitrile (10.2 g) and 6N-hydrochloric acid (6.83 ml) in ethyl acetate (50 ml) was stirred for 1.5 hours at room temperature. The resulting precipitate was filtered off and to the filtrate was added to ethyl acetate (100 ml). The resulting solution was washed in turn with water (50 ml x 3), brine (50 ml), saturated sodium hydrogen carbonate in water (50 ml x 2) and brine (50 ml), and dried over magnesium sulfate. Evaporation of the solvent gave an oil, which was chromatographed on silica gel eluting in turn with 50% ethyl acetate in n-hexane and ethyl acetate to give N-(allyloxycarbonyl)-N-(2-hydroxyethyl)aminoacetonitrile (5.71 g).

NMR ($CDCl_3$, δ) : 2.0 (1H, br s), 3.58 (2H, t, J=5.2Hz), 3.87 (2H, t, J=5.2Hz), 4.25 (2H, s), 4.40-4.50 (2H, m), 5.00-5.20 (2H, m), 5.60-6.00 (1H, m)

Preparation 10-3)

To a solution of N-(allyloxycarbonyl)-N-(2-hydroxyethyl)aminoacetonitrile (5.65 g) and pyridine (3 ml) in tetrahydrofuran (60 ml) was added dropwise allyl chloroformate (3.6 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stand for 12 hours. The reaction mixture was poured into ethyl acetate

(300 ml), washed in turn with water, 1N-hydrochloric acid, brine, saturated sodium hydrogen carbonate in water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (250 ml) eluting in turn with 20% ethyl acetate in n-hexane and 50% ethyl acetate in n-hexane to give N-(2-allyloxycarbonyloxyethyl)-N-(allyloxycarbonyl)amino-acetonitrile (4.52 g).

NMR ($CDCl_3$, δ) : 3.70 (2H, t, J=5.2Hz), 4.20-4.40 (4H, m), 4.60-4.70 (4H, m), 5.20-5.45 (4H, m), 5.80-6.00 (2H, m)

Preparation 10-4)

Ethyl 2-[N-(2-allyloxycarbonyloxyethyl)-N-(allyloxycarbonyl)amino]acetimidate hydrochloride was obtained in 98.5% yield in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.33 (3H, t, J=7.0Hz), 3.50-3.70 (2H, m), 4.20-4.30 (2H, m), 4.40-4.65 (6H, m), 5.10-5.40 (4H, m), 5.80-6.00 (2H, m)

Preparation 11

To a solution of 2-iodoethanol (7.8 ml) and imidazole (15.83 g) in dichloromethane (100 ml) was added tert-butyldimethylsilyl chloride (15.83 g) by portions at 0°C. After two hours, the precipitate was filtered off, and the filtrate was washed in turn with 1N-hydrochloric acid, brine, saturated sodium hydrogen carbonate in water and brine. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (300 ml) eluting with a mixture of hexane and ethyl acetate (9:1 to 4:1, V/V) to give 2-tert-butyldimethylsilyloxy-1-iodoethane (26.93 g).

NMR ($CDCl_3$, δ) : 0.08 (6H, s), 0.90 (9H, s), 3.20 (2H, t, J=6.75Hz), 3.83 (2H, t, J=6.74Hz)

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Preparation 12-1)

A mixture of methyl cyanoacetate (12.9 ml), N-(4-(t-butoxycarbonylamino)butyl)amine (21.1 g) and triethylamine (23 ml) in methanol (60 ml) was allowed to stand at ambient temperature for 15 hours. Evaporation of the mixture gave a residue which was chromatographed on silica gel (800 ml) eluting with a mixture of n-hexane and ethyl acetate (7:3) to give N-(4-(t-butoxycarbonylamino)-butyl)-2-cyanoacetamide (17.3 g).

NMR ($CDCl_3$, δ) : 1.45 (9H, s), 1.48-1.62 (4H, m), 3.15 (2H, q, J=6.5Hz), 3.33 (2H, q, J=6.5Hz), 3.38 (2H, s), 4.66, 6.74 (total 2H, each br s)

Preparation 12-2)

To a solution of N-(4-(t-butoxycarbonylamino)butyl)-2-cyanoacetamide (16.19 g) in a mixture of dichloromethane were added anisole (16 ml) and trifluoroacetic acid (30 ml) at 0°C. The resulting mixture was stirred at ambient temperature for 1.5 hours. After evaporation of the solvent, the residue was taken up into a mixture of cold water (200 ml) and ethyl acetate (200 ml). To the separated aqueous layer was added tetrahydrofuran (100 ml), and to the mixture was added allyl chloroformate (7.4 ml) while adjusting pH to around 9 with 3N aqueous potassium hydroxide at 0°C. Slight evaporation gave an aqueous residue, which was extracted several times with ethyl acetate, and the combined organic layer was dried over magnesium sulfate. Evaporation of the solution gave a residue which was chromatographed on silica gel (300 ml) eluting with a mixture of n-hexane and ethyl acetate (1:1, V/V) to give N-(4-(allyloxycarbonylamino)butyl)-2-cyanoacetamide (8.37 g).

IR (Nujol) : 3270, 2260, 1650 cm-1

NMR (DMSO-d_6, δ) : 1.3-1.5 (4H, m), 2.8-3.15 (4H,

m), 3.61 (2H, s), 4.4-4.5 (2H, m), 5.1-5.3 (2H, m), 5.7-6.05 (1H, m), 7.21 (1H, br t), 8.33 (1H, br t)

Preparation 12-3)

Ethyl 2-[N-(4-(allyloxycarbonylamino)butyl)-carbamoyl]acetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.25-1.5 (7H, m), 2.9-3.2 (4H, m), 3.69 (2H, s), 4.3-4.5 (4H, m), 5.05-5.35 (2H, m), 5.8-6.0 (1H, m)

Preparation 13-1)

To a mixture of 5-(allyloxycarbonylamino)pentanoic acid (25.5 g) and N-(t-butoxycarbonyl)piperazine (23.61 g) in dichloromethane (250 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(WSC) hydrochloride (24.3 g) at 0°C. The mixture was stirred at ambient temperature for one hour. Evaporation of the solvent gave a residue which was taken up into a mixture of water (200 ml) and ethyl acetate (200 ml). The separated organic layer was washed in turn with hydrochloric acid (1N, 50 ml), water, aqueous sodium bicarbonate (50 ml), and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 1-(5-(allyloxycarbonylamino)pentanoyl)-4-t-butoxycarbonyl-piperazine (46.2 g).

This compound was immediately used as the starting compound for the next step.

Preparation 13-2)

To a solution of 1-(5-(allyloxycarbonylamino)-pentanoyl)-4-t-butoxycarbonylpiperazine (44.62 g) in acetonitrile (400 ml) was added p-toluenesulfonic acid monohydrate (69.0 g), and the resultant mixture was stirred at ambient temperature for 4 hours. Evaporation

of the solvent gave a residue which was taken up into methanol (100 ml), and to the solution was added triethylamine (60 ml) and methyl cyanoacetate (40 ml). The resultant mixture was stirred at 40°C for 3 days, at ambient temperature for 10 days and then at 70°C for 2 days and evaporated. The residue was chromatographed on silica gel (6 ℓ) eluting with a mixture of n-hexane, ethyl acetate and ethanol (8:2:0 to 0:85:15, V/V) to give 1-(5-allyloxycarbonylamino)pentanoyl)-4-(cyanoacetyl)piperazine (19.87 g).

IR (Nujol) : 3300, 2250, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.6 (4H, m), 2.2-2.4 (2H, m), 2.85-3.05 (2H, m), 3.2-3.6 (8H, m), 4.07 (2H, s), 4.4-4.5 (2H, m), 5.1-5.35 (2H, m), 5.7-6.05 (1H, m), 7.19 (1H, br t)

Preparation 13-3)

Ethyl 2-[4-(5-(allyloxycarbonylamino)pentanoyl)-piperazin-1-ylcarbonyl]acetimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.3-1.6 (7H, m), 2.2-2.45 (2H, m), 2.9-3.1 (2H, m), 3.3-3.7 (8H, m), 4.0-4.2 (2H, m), 4.4-4.6 (5H, m), 5.1-5.35 (2H, m), 5.9-6.05 (1H, m)

Preparation 14

Ethyl 3-(benzyloxycarbonylamino)propanimidate hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.32 (3H, t, J=7Hz), 2.76 (2H, t, J=6.4Hz), 3.25-3.45 (2H, m), 4.42 (2H, q, J=7Hz), 5.03 (2H, s), 7.35 (5H, s), 7.62 (1H, t, J=5.6Hz)

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Preparation 15

Ethyl 3-(p-nitrobenzyloxycarbonylamino)propanimidate hydrochloride (18.29 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.33 (3H, t, J=7.0Hz), 2.77 (2H, t, J=6.3Hz), 3.1-3.5 (2H, m), 4.38 (2H, q, J=7.0Hz), 5.19 (2H, s), 7.60 (2H, d, J=8.7Hz), 7.80 (1H, t, J=5.8Hz), 8.25 (2H, d, J=8.7Hz)

Preparation 16-1)

To a stirred suspension of sodium hydride (dispersion in oil, 62%, 2.31 g) in N,N-dimethylformamide (60 ml) was added by portions 3-(t-butoxycarbonylamino)propanenitrile (9.98 g) at ambient temperature. After vigorous stirring at ambient temperature for 4 hours, the resulting solution was cooled to 0°C, and to the solution was added 1-t-butyldimethylsilyloxy-2-iodoethane (17.6 g), and the mixture was allowed to warm to ambient temperature for 3 hours. The reaction mixture was taken up into a mixture of cold water (300 ml) and ethyl acetate (300 ml). The organic layer was separated, washed in turn well with water and brine, dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silica gel (300 ml) eluting with a mixture of n-hexane and ethyl acetate (95:5 to 80:20) to give 3-[N-t-butoxycarbonyl-N-{2-(t-butyldimethylsilyloxy)-ethyl}amino]propanenitrile (10.5 g).

NMR ($CDCl_3$, δ) : 0.05 (6H, s), 0.90 (9H, s), 1.45, 1.47 (total 9H, each s), 2.5-2.6 (2H, m), 3.37 (2H, t, J=5.0Hz), 3.57 (2H, t, J=5.0Hz), 3.55-3.75 (2H, m)

Preparation 16-2)

To a stirred solution of 3-[N-t-butoxycarbonyl-N-{2-

(t-butyldimethylsilyloxy)ethyl}aminopropanenitrile (10.0 g) in tetrahydrofuran (70 ml) was added aqueous tetra-n-butylammonium fluoride (70%, 12.5 g) at ambient temperature. After stirring at ambient temperature for 30 minutes, the reaction mixture was taken up into a mixture of water (200 ml), ethyl acetate (100 ml) and hexane (100 ml). The organic layer was separated, washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1 to 0:10, V/V) to give 3-(N-t-butoxycarbonyl-N-(2-hydroxyethyl)amino)propanenitrile (5.07 g).

NMR ($CDCl_3$, δ) : 1.48 (9H, s), 2.09 (1H, br s), 2.65 (2H, br s), 3.45 (2H, t, J=5.0Hz), 3.57 (2H, t, J=6.8Hz), 3.77 (2H, t, J=5.0Hz)

Preparation 16-3)

3-(N-t-Butoxycarbonyl-N-(2-hydroxyethyl)amino)-propanenitrile (5.05 g) was dissolved in trifluoroacetic acid (25 ml) at ambient temperature. After 2 hours' standing, solvent was removed under reduced pressure. The residue was taken up into a mixture of ethanol (1.5 ml) and chloroform (40 ml). To the mixture was introduced hydrogen chloride (1.7 g) at 0°C, and the resulting mixture was allowed to stand at 5°C for 10 hours. Evaporation of the solvent gave ethyl 3-((2-hydroxyethyl)-amino)propanimidate dihydrochloride.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7.0Hz), 4.42 (2H, q, J=7.0Hz)

Preparation 17-1)

To a solution of 3-aminopropanenitrile (20 ml) in methyl ethyl ketone (80 ml) was added iodoacetamide (25.0 g) at ambient temperature. After stirring for 15 hours, the resulting viscous oil was collected by decantation,

and taken up into a mixture of cold water (100 ml) and tetrahydrofuran (200 ml). To the mixture was added by portions benzyloxycarbonyl chloride (38.8 ml) while adjusting pH to around 9 with aqueous potassium hydroxide (3N) at 0°C. Evaporation of the solvent gave a residue which was chromatographed on silica gel (800 ml) eluting with a mixture of ethyl acetate and methanol (10:0 to 8:2, V/V) to give 3-(N-carbamoylmethyl-N-benzyloxycarbonyl-amino)propanenitrile (16.6 g).

NMR ($CDCl_3$, δ) : 2.70 (2H, br s), 3.66 (2H, t, J=6.5Hz), 4.02 (2H, s), 5.17 (2H, s), 5.61, 6.0 (total 2H, each br s), 7.36 (5H, s)

Preparation 17-2)

To a solution of 3-(N-carbamoylmethyl-N-benzyloxy-carbonylamino)propanenitrile (16.6 g) in a mixture of tetrahydrofuran (250 ml) and methanol (60 ml) were added acetic acid (7.2 ml) and palladium on carbon (20%, 50% wet, 3.3 g) under nitrogen atmosphere. The resulting mixture was stirred under hydrogen atmosphere for 2 hours at ambient temperature. After the removal of catalyst by filtration, solvents were evaporated to give 3-(carbamoylmethylamino)propanenitrile acetate which is used for next step without further purification.

NMR (DMSO-d_6, δ) : 2.55-2.65 (2H, m), 2.65-2.80 (2H, m), 3.08 (2H, s)

Preparation 17-3)

Ethyl 3-(carbamoylmethylamino)propanimidate dihydrochloride (13.55 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7.0Hz), 4.45 (2H, q, J=7.0Hz)

Preparation 18-1)

INSDOCID: <WO__ 9323402A1_I_>

3-(N-Carbamoylmethyl-N-allyloxycarbonylamino)-propanenitrile (19.5 g) was obtained from 3-amino-propanenitrile (20 ml), iodoacetamide (25 g) and allyloxycarbonyl chloride (33 ml) in substantially the same method as that of Preparation 14-1).

IR (Nujol) : 3370, 3150, 1650 cm-1

NMR (DMSO-d_6, δ) : 2.65-2.8 (2H, m), 3.4-3.6 (2H, m), 3.88, 3.84 (total 2H, each s), 4.4-4.6 (2H, m), 5.1-5.4 (2H, m), 5.7-6.1 (1H, m), 7.05, 7.41 (total 2H, each br s)

Preparation 18-2)

Ethyl 3-(N-allyloxycarbonyl-N-carbamoylmethylamino)-propanimidate hydrochloride (11.36 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.38 (3H, t, J=7.0Hz), 2.7-2.9 (2H, m), 3.5-3.8 (2H, m), 3.8-4.1 (2H, m), 4.39 (2H, q, J=7.0Hz), 4.45-4.6 (2H, m), 5.0-5.4 (2H, m), 5.7-6.1 (1H, m)

Preparation 19-1)

A mixture of 3-(methylamino)propanenitrile (12.6 ml), iodoacetamide (25 g) and potassium carbonate (11.2 g) in methyl ethyl ketone (50 ml) was stirred at ambient temperature for 2.5 hours. To that mixture was added triethylamine (9.5 ml) and allyloxycarbonyl chloride (8.3 ml). Evaporation of the mixture gave a residue which was chromatographed on silica gel (800 ml) eluting with a mixture of chloroform, methanol and aqueous ammonium hydroxide (18%) (9:1:0.1, V/V). The objective fractions were collected and evaporated to give a residue which was taken up into ethyl acetate (1 ℓ) and washed with brine (10 ml x 2). Evaporation and trituration with diisopropyl ether gave 3-(N-carbamoylmethyl-N-methylamino)-propanenitrile (9.84 g).

3NSDOCID: <WO 9323402A1 >

IR (Nujol) : 3380, 3150, 2240, 1600 cm-1
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.55 (2H, t, J=6Hz), 2.78 (2H, t, J=6Hz), 3.10 (2H, s), 5.76, 7.08 (total 2H, each br s)

Preparation 19-2)

Ethyl 3-(N-carbamoylmethyl-N-methylamino)-propanimidate dihydrochloride was obtained in substantially the same manner as that of Preparation 1.
NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 2.87 (3H, s), 3.0-3.7 (4H, m), 3.95 (2H, s), 4.47 (2H, q, J=7Hz)

Preparation 20-1)

3-(N-(2-t-butyldimethylsilyloxyethyl)-N-methylamino)-propanenitrile (23.25 g) was obtained in substantially the same manner as that of Preparation 19-1).

This compound was immediately used as the starting compound for the next step.

Preparation 20-2)

3-(N-(2-t-Butyldimethylsilyloxyethyl)-N-methylamino)-propanenitrile (11.6 g) was dissolved in ethanol (20 ml) containing about 10% (W/W) of hydrogen chloride at ambient temperature. After standing at ambient temperature for 2 hours, solvent was removed by evaporation, and the remaining acidic media was removed by azeotropy with toluene to give 3-(N-(2-hydroxyethyl)-N-methylamino)-propanenitrile hydrochloride (6.83 g).
IR (Nujol) : 3250, 2600, 2250 cm-1
NMR (D_2O, δ) : 2.81 (3H, s), 3.1-3.3 (4H, m), 3.35-3.6 (2H, m), 3.77 (2H, t, J=5.2Hz)

Preparation 20-3)

Ethyl 3-(N-(2-hydroxyethyl)-N-methylamino)-

propanimidate dihydrochloride (12.1 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 2.80 (3H, s), 3.0-3.8 (8H, m), 4.46 (2H, q, J=7Hz)

Preparation 21-1)

N-(3-Cyanopropyl)-N-(N-(2-hydroxyethyl)carbamoylmethyl)-N,N-dimethylammonium bromide (5.74 g) was obtained in substantially the same manner as that of Preparation 8-1).

NMR (DMSO-d_6, δ) : 1.98-2.17 (2H, m), 2.65 (2H, t, J=7Hz), 3.23 (6H, s), 3.10-3.30 (2H, m), 3.39-3.86 (4H, m), 4.14 (2H, s), 4.78 (1H, t, J=5Hz), 8.67 (1H, br t, J=6Hz)

Preparation 21-2)

Ethyl 4-[N,N-dimethyl-N-{N-(2-hydroxyethyl)carbamoylmethyl}ammonio]butyrimidate bromide hydrochloride (7.9 g) was obtained in substantially the same manner as that of Preparation 8-2).

NMR (DMSO-d_6, δ) : 1.41 (3H, t, J=7Hz), 1.8-2.2 (2H, m), 2.65-2.95 (2H, m), 3.05-3.80 (12H, m), 4.1-4.8 (4H, m), 8.89 (1H, br s)

Preparation 22-1)

N-(2-Hydroxymethyl)-N-(3-cyanopropyl)-N,N-dimethylammonium bromide (6.86 g) was obtained in substantially the same method as that of Preparation 8-1).

NMR (DMSO-d_6, δ) : 1.96-2.15 (2H, m), 2.63 (2H, t, J=7Hz), 3.13 (6H, s), 3.37-3.50 (4H, m), 3.70-3.95 (2H, m), 5.31 (1H, t, J=5Hz)

Preparation 22-2)

Ethyl 4-(N,N-dimethyl-N-(2-hydroxyethyl)ammonio)-

butyrimidate bromide hydrochloride (7.77 g) was obtained in substantially the same manner as that of Preparation 8-2).

NMR (DMSO-d_6, δ) : 1.42 (3H, t, J=7Hz), 2.0-2.2 (2H, m), 2.77 (2H, t, J=6.7Hz), 3.16 (6H, s), 3.3-3.65 (4H, m), 3.7-3.95 (2H, m), 4.48 (2H, q, J=7Hz)

Preparation 23-1)

To a stirred solution of 2-(N,N-dimethylamino)ethanol (5 ml) in dichloromethane (50 ml) was added dropwise trichloroacetylisocyanate (6.2 ml) at 0°C. After stirring at 0°C for 30 minutes, the resultant precipitate was collected by filtration, which was taken up into methanol (100 ml) and the solution was allowed to stand for 10 hours. Evaporation of the solvent gave N-(2-carbamoyloxyethyl)-N,N-dimethylamine.

NMR (DMSO-d_6, δ) : 2.14 (6H, s), 2.40 (2H, t, J=6Hz), 3.96 (2H, t, J=6Hz), 6.46 (2H, br s)

Preparation 23-2)

N-(2-Carbamoyloxyethyl)-N-(3-cyanopropyl)-N,N-dimethylammonium bromide was obtained in substantially the same manner as that of Preparation 8-1).

NMR (DMSO-d_6, δ) : 1.95-2.15 (2H, m), 6.14 (2H, t, J=7Hz), 3.13 (6H, s), 3.30-3.50 (2H, m), 3.50-3.75 (2H, m), 4.20-4.40 (2H, m), 6.77 (2H, br s)

Preparation 23-3)

Ethyl 4-(N-(2-carbamoyloxyethyl)-N,N-dimethylammonio)butyrimidate bromide hydrochloride (9.9 g) was obtained in substantially the same manner as that of Preparation 8-2).

NMR (DMSO-d_6, δ) : 1.38 (3H, t, J=7Hz), 2.0-2.25

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(2H, m), 2.80 (2H, t, J=7Hz), 3.16 (6H, s), 3.34-3.55 (2H, m), 3.55-3.75 (2H, m), 4.34 (2H, m), 4.48 (2H, q, J=7Hz), 4.68 (2H, br s)

Preparation 24-1)

To a stirred solution of methyl cyanoacetate (5.4 ml) in methanol (30 ml) was added dropwise N,N-dimethylethylenediamine (6.42 g) at ambient temperature. After one hour, the mixture was evaporated, and the residue was chromatographed on silica gel (150 ml) eluting with methanol to give N-cyanoacetyl-N',N'-dimethylethylenediamine (7.0 g).

NMR ($CDCl_3$, δ) : 2.24 (6H, s), 2.44 (2H, t, J=6Hz), 3.30-3.49 (4H, m), 6.73 (1H, br s)

Preparation 24-2)

N-(2-Cyanoacetamidoethyl)-N,N-dimethyl-N-(2-hydroxyethyl)ammonium iodide (2.15 g) was obtained from N-cyanoacetyl-N',N'-dimethylethylenediamine (2.0 g) and iodoethanol (1.3 ml) in substantially the same method as that of Preparation 8-1).

NMR (DMSO-d_6, δ) : 3.13 (6H, s), 3.36 (2H, s), 3.40-3.80 (6H, m), 3.75-3.95 (2H, m), 5.29 (1H, t, J=5Hz), 8.50 (1H, br s)

Preparation 24-3)

Ethyl 2-[N-[2-{N,N-dimethyl-N-(2-hydroxyethyl)-ammonio}ethyl]carbamoyl]acetimidate iodide hydrochloride (2.96 g) was obtained in substantially the same manner as that of Preparation 8-2).

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 3.08-3.20 (8H, m), 3.20-3.80 (6H, m), 3.80-4.05 (2H, m), 4.45 (2H, q, J=7Hz)

Preparation 25

INSDOCID: <WO 9323402A1 >

Ethyl 3-(3-pyridyl)propenimidate dihydrochloride was obtained from 3-(2-cyanoethenyl)pyridine (4.0 g) in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.47 (3H, t, J=7Hz), 3.44 (2H, q, J=7Hz), 7.48 (1H, d, J=16.3Hz), 8.1-8.25 (2H, m), 8.8-9.3 (3H, m)

Preparation 26-1)

To a solution of 3-(2-cyanoethenyl)Pyridine (6.0 g) in acetone (50 ml) was added iodomethane (14 ml). After stirring at ambient temperature for 15 hours, the resulting precipitate was collected by filtration, washed with acetone to give 3-(2-cyanoethenyl)-1-methyl pyridinium iodide (12.3 g).

NMR (DMSO-d_6, δ) : 4.37 (3H, s), 6.89 (1H, d, J=16.7Hz), 7.83 (1H, d, J=16.7Hz), 8.22 (1H, dd, J=6Hz, 8Hz), 8.80 (1H, d, J=8Hz), 9.03 (1H, d, J=6Hz), 9.32 (1H, s)

Preparation 26-2)

Ethyl 3-(1-methyl-3-pyridinio)propenimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.46 (3H, t, J=7Hz), 4.40 (3H, s), 4.59 (2H, q, J=7Hz), 7.34 (1H, d, J=16.2Hz), 8.06 (1H, d, J=16.2Hz), 8.25 (1H, dd, J=6Hz, 8Hz), 8.83 (1H, d, J=8Hz), 9.09 (1H, d, J=6Hz), 9.50 (1H, s)

Preparation 27-1)

A mixture of 3-(2-cyanoethenyl)pyridine (2.0 g) and iodoacetamide (5.7 g) in acetone (30 ml) was stirred at ambient temperature for 2 days. The resulting precipitate was collected by filtration, washed with acetone, and dried to give 1-carbamoylmethyl-3-(2-cyanoethenyl)-

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Pyridinium iodide (4.23 g).

NMR (DMSO-d_6, δ) : 5.41 (2H, s), 6.86 (1H, d, J=16.7Hz), 7.82 (1H, d, J=16.7Hz), 7.78 (1H, br s), 8.08 (1H, br s), 8.27 (1H, dd, J=6Hz, 8Hz), 8.89 (1H, d, J=8Hz), 9.01 (1H, d, J=6Hz), 9.29 (1H, s)

Preparation 27-2)

Ethyl 3-(1-carbamoylmethyl-3-pyridinio)propenimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.47 (3H, t, J=7Hz), 5.50 (2H, s), 7.28 (1H, d, J=16.2Hz), 8.07 (1H, d, J=16.2Hz), 8.1-8.4 (1H, m), 8.8-9.6 (3H, m)

Preparation 28-1)

3-(2-Cyanoethyl)-1-methylpyridinium iodide (22.81 g) was obtained from 3-(2-cyanoethyl)pyridine (11.98 g) and iodomethane (20 ml) in substantially the same manner as that of Preparation 26-1).

NMR (DMSO-d_6, δ) : 2.9-3.1 (2H, m), 3.1-3.25 (2H, m), 4.35 (3H, s), 8.14 (1H, dd, J=6Hz, 8Hz), 8.56 (1H, d, J=8Hz), 8.93 (1H, d, J=6Hz), 9.07 (1H, s)

Preparation 28-2)

Ethyl 3-(1-methyl-3-pyridinio)propanimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.32 (3H, t, J=7Hz), 3.1-3.3 (4H, m), 4.33 (3H, s), 4.37 (2H, q, J=7Hz), 8.10 (1H, dd, J=6Hz, 8Hz), 8.55 (1H, d, J=8Hz), 8.93 (1H, d, J=6Hz), 9.21 (1H, s)

Preparation 29-1)

A solution of chloroacetonitrile (4 ml) and 1-methylimidazole (5.03 ml) in acetone (30 ml) was heated to 60°C for 3 hours. The resulting precipitate was collected by filtration, washed with diisopropyl ether, and dried to give 1-cyanomethyl-3-methylimidazolium chloride (2.83 g). This product was immediately used as the starting compound for the next step.

Preparation 29-2)

Ethyl 2-[3-methyl-1-imidazolio]acetimidate chloride hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.25 (3H, t, J=7Hz), 3.93 (3H, s), 4.20 (2H, q, J=7Hz), 5.32 (2H, s), 7.7-7.8 (2H, m), 9.28 (1H, s)

Preparation 30-1)

A solution of 4-bromobutanenitrile (5.6 ml) and thiazole (4 ml) in toluene (20 ml) was heated to 120°C for 10 hours. The resulting precipitate was collected by filtration, washed with diethyl ether, and dried to give 3-(3-cyanopropyl)thiazolium bromide (6.25 g).

IR (Nujol) : 2250 cm^{-1}

NMR (DMSO-d_6, δ) : 2.1-2.4 (2H, m), 2.67 (2H, t, J=7Hz), 4.68 (2H, t, J=7Hz), 8.39-8.44 (1H, m), 8.65-8.70 (1H, m), 10.30-10.36 (1H, m)

Preparation 30-2)

Ethyl 4-(3-thiazolio)butanimidate bromide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.36 (3H, t, J=7Hz), 4.43 (2H, q, J=7Hz), 8.38-8.43 (1H, m), 8.60-8.72 (1H, m), 10.42-10.44 (1H, m)

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Preparation 31-1)

A mixture of 4-bromobutanenitrile (4.47 g) and imidazole (4.11 g) was heated to 100°C for 3 hours. After cooling, the mixture was chromatographed on silica gel (500 ml) eluting with a mixture of chloroform and methanol (10:0 to 7:3, V/V) to give 4-(imidazol-1-yl)butanenitrile (2.86 g).

NMR ($CDCl_3$, δ) : 1.95-2.11 (2H, m), 2.33 (2H, t, J=6.5Hz), 4.13 (2H, t, J=6.5Hz), 6.95 (1H, s), 7.09 (1H, s), 7.71 (1H, s)

Preparation 31-2)

Ethyl 4-(imidazol-1-yl)butanimidate dihydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.35 (3H, t, J=7Hz), 2.18-2.23 (2H, m), 2.72 (2H, t, J=7.5Hz), 4.1-4.6 (4H, m), 7.69 (1H, s), 7.89 (1H, s), 9.35 (1H, s)

Preparation 31-3)

A mixture of 4-(imidazol-1-yl)butanenitrile (3.5 g) and 2-iodoethanol (3.1 ml) in methyl ethyl ketone (10 ml) was heated to 100°C for 4 hours. The resulting oil was separated by decantation, washed with methyl ethyl ketone and diisopropyl ether to give 1-hydroxyethyl-3-(3-cyanopropyl)imidazolium iodide (7.4 g, 93%).

NMR (DMSO-d_6, δ) : 2.0-2.25 (2H, m), 2.58 (2H, t, J=7Hz), 3.73 (2H, t, J=5Hz), 4.15-4.35 (4H, m), 7.77-7.79 (1H, m), 7.82-7.84 (1H, m), 9.21 (1H, s)

Preparation 31-4)

Ethyl 4-(3-(2-hydroxyethyl)-1-imidazolio)butanimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

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NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 2.0-2.3 (2H, m), 2.71 (2H, t, J=7Hz), 3.73 (2H, t, J=5Hz), 4.0-4.6 (6H, m), 7.54-7.86 (2H, m), 9.27 (1H, s)

Preparation 32-1)

1-(3-Cyanopropyl)-2-methylimidazole (4.35 g) was obtained from 4-bromobutanenitrile (5.9 g) and 2-methylimidazole (6.57 g) in substantially the same method as that of Preparation 31-1).

NMR ($CDCl_3$, δ) : 2.0-2.16 (2H, m), 2.35 (2H, t, J=7Hz), 2.39 (3H, s), 4.03 (2H, t, J=7Hz), 6.84 (1H, d, J=1.4Hz), 6.94 (1H, d, J=1.4Hz)

Preparation 32-2)

Ethyl 4-(2-methylimidazol-1-yl)butanimidate dihydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.36 (1H, t, J=7Hz), 2.0-2.3 (2H, m), 2.69 (3H, s), 2.79 (3H, t, J=7.5Hz), 4.22 (3H, t, J=7Hz), 4.46 (2H, q, J=7Hz), 7.60 (1H, dd, J=1Hz, 4Hz), 7.90 (1H, dd, J=1Hz, 4Hz)

Preparation 33-1)

A mixture of 1-methyl-4-(hydroxymethyl)imidazole (2.5 g) and 4-bromobutanenitrile (2.2 ml) in toluene (15 ml) was heated to 80°C for 4 hours. The resultant oil was separated by decantation and washed with toluene to give 3-(3-cyanopropyl)-4-hydroxymethyl-1-methylimidazolium bromide (2.98 g).

NMR (DMSO-d_6, δ) : 2.0-2.15 (2H, m), 2.65 (3H, t, J=7.2Hz), 3.83 (3H, s), 4.26 (2H, t, J=7.2Hz), 4.56 (2H, d, J=5.2Hz), 5.69 (1H, t, J=5.2Hz), 7.66 (1H, d, J=1.4Hz), 9.21 (1H, d, J=1.4Hz)

Preparation 33-2)

Ethyl 4-(4-hydroxymethyl-1-methyl-3-imidazolio)-

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butanimidate bromide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.37 (3H, t, J=7Hz), 2.1-2.3 (2H, m), 2.78 (2H, t, J=7.5Hz), 3.85 (3H, s), 4.2-4.6 (6H, m), 7.66 (1H, d, J=1.4Hz), 9.30 (1H, d, J=1.4Hz)

Preparation 34-1)

A solution of 6-bromohexanenitrile (5.0 g) and 1-methylimidazole (3.4 ml) in toluene (5 ml) was heated to 65°C for 2 hours. The resulting oil was separated by decantation, washed well with toluene to give 3-methyl-1-(5-cyanopentyl)imidazolium bromide (7.35 g).

NMR (DMSO-d_6, δ) : 1.2-1.4 (2H, m), 1.5-1.7 (2H, m), 1.7-1.9 (2H, m), 2.51 (2H, t, J=7Hz), 3.87 (3H, s), 4.20 (2H, t, J=7Hz), 7.74-7.77 (1H, m), 7.81-7.84 (1H, m), 9.25 (1H, s)

Preparation 34-2)

Ethyl 6-(3-methyl-1-imidazolio)hexanimidate bromide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.1-1.45 (5H, m), 1.5-2.0 (4H, m), 2.68 (2H, t, J=7Hz), 3.89 (3H, s), 4.22 (2H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 7.76 (1H, s), 7.85 (1H, s), 9.40 (1H, s)

Preparation 35-1)

To a stirred solution of 5-hydroxymethyl-1-methylimidazole (15.56 g) in dichloromethane (78 ml) were added thionyl chloride (10.2 ml) and five drops of N,N-dimethylformamide at -30°C - -20°C. The reaction mixture was allowed to warm to ambient temperature and evaporated. The residue was chromatographed on silica gel

(600 ml) eluting with a mixture of chloroform and methanol (100:0 to 94:6, V/V) to give 5-chloromethyl-1-methylimidazole hydrochloride (5.65 g).

NMR ($CDCl_3$, δ) : 4.00 (3H, s), 4.92 (2H, s), 7.69 (1H, s), 8.99 (1H, s)

Preparation 35-2)

5-Cyanomethyl-1-methylimidazole (5.7 g) was obtained in substantially the same method as that of Preparation 41-2).

NMR ($CDCl_3$, δ) : 3.69 (3H, s), 3.72 (2H, s), 7.02 (1H, s), 7.48 (1H, s)

Preparation 35-3)

To a solution of 5-cyanomethyl-1-methylimidazole (5.61 g) in acetone (45 ml) was added iodomethane (10 ml) at ambient temperature. After stirring at ambient temperature for 10 hours, the resulting precipitate was collected by filtration, washed with acetone, and dried to give 4-cyanomethyl-1,3-dimethylimidazolium iodide (9.41 g).

NMR (DMSO-d_6, δ) : 3.82 (3H, s), 3.85 (3H, s), 4.38 (2H, s), 7.76 (1H, s), 9.12 (1H, s)

Preparation 35-4)

Ethyl 2-(1,3-dimethyl-4-imidazolio)acetimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.34 (3H, t, J=7Hz), 4.48 (2H, q, J=7Hz)

Preparation 36-1)

2-Chloromethyl-1-methylimidazole hydrochloride (11.85 g) was obtained in substantially the same method as that of Preparation 35-1).

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NMR (MeOD, δ) : 3.97 (3H, s), 5.08 (2H, s), 7.59 (1H, d, J=2Hz), 7.65 (1H, d, J=2Hz)

Preparation 36-2)

2-Cyanomethyl-1-methylimidazole (206 mg) was obtained in substantially the same manner as that of Preparation 41-2).

IR (Nujol) : 2200 cm-1

NMR ($CDCl_3$, δ) : 3.71 (3H, s), 3.89 (2H, s), 6.91 (1H, d, J=1Hz), 6.97 (1H, d, J=1Hz)

Preparation 36-3)

2-Cyanomethyl-1,3-dimethylimidazolium iodide (8.15 g) was obtained in substantially the same manner as that of Preparation 35-3).

IR (Nujol) : 2250 cm-1

NMR (DMSO-d_6, δ) : 3.88 (6H, s), 4.80 (2H, s), 7.77 (2H, s)

Preparation 36-4)

Ethyl 2-(1,3-dimethyl-2-imidazolio)acetimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7Hz), 3.80 (6H, s), 4.17 (2H, q, J=7Hz), 4.49 (2H, s), 8.37 (2H, s)

Preparation 37-1)

To a suspension of sodium hydride (62% dispersion in oil, 2.11 g) in N,N-dimethylformamide (180 ml) were added in turn diethyl cyanomethylphosphate (8.6 ml) and 1-(triphenylmethyl)imidazole-4-carbaldehyde (14.9 g) at 0°C. The mixture was heated to reflux for 3 hours, and was taken up into a mixture of cold water (150 ml) and ethyl acetate (100 ml). The resultant precipitate was

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filtered off, and the filtrate was concentrated to give a residue which was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (7:3, V/V) to give 4-(2-cyanoethenyl)-1-(triphenylmethyl)-imidazole (9.7 g).

NMR (DMSO-d_6, δ) : 6.04 (1H, d, J=16Hz), 7.0-7.6 (18H)

Preparation 37-2)

A solution of 4-(2-cyanoethenyl)-1-(triphenylmethyl)-imidazole (9.64 g) in a mixture of methanol (80 ml) and acetic acid (20 ml) was heated to 80°C for 8 hours. Solvents were removed by evaporation and the residue was washed well with n-hexane to give 4-(2-cyanoethenyl)-imidazole acetate, which was used without purification for the next step.

NMR (DMSO-d_6, δ) : 6.00 (1H, d, J=16Hz), 7.48 (1H, d, J=16Hz), 7.49 (1H, s), 7.78 (1H, s)

Preparation 37-3)

To a stirred solution of 4-(2-cyanoethenyl)imidazole (13.6 g crude) in methanol (130 ml) was added palladium on carbon (10%, 50% wet, 2.5 g). The mixture was allowed to stir under atmospheric pressure of hydrogen at ambient temperature for 5 hours. The catalyst was filtered off and the filtrate was evaporated to give 4-(2-cyanoethyl)-imidazole acetate (4.47 g).

NMR (DMSO-d_6, δ) : 2.35-2.65 (4H, m), 6.68 (1H, s), 7.49 (1H, s)

Preparation 37-4)

Ethyl 3-(imidazol-4-yl)propanimidate dihydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7Hz),

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4.44 (2H, q, J=7Hz)

Preparation 38-1)

2-(2-Cyanoethenyl)-1-methylimidazole (1.14 g) was obtained from diethyl cyanomethylphosphate (17.54 ml) and 1-methylimidazole-2-carbaldehyde (16.8 g, crude) in substantially the same method as that of Preparation 73-1).

NMR ($CDCl_3$, δ) : 3.74 (3H, s), 6.32 (1H, d, J=16Hz), 7.01 (1H, d, J=0.7Hz), 7.15 (1H, d, J=0.7Hz), 7.20 (1H, d, J=16Hz)

Preparation 38-2)

To a stirred solution of 2-(2-cyanoethenyl)-1-methylimidazole (2.3 g) in acetone (5 ml) was added iodomethane (5 ml) at ambient temperature. After stirring at ambient temperature for 3 days, the resulting precipitate was collected by filtration, washed with acetone and dried to give 2-(2-cyanoethenyl)-1,3-dimethylimidazolium iodide (3.3 g).

NMR (DMSO-d_6, δ) : 3.93 (6H, s), 6.75 (1H, d, J=16.8Hz), 7.87 (1H, d, J=16.8Hz), 7.89 (2H, s)

Preparation 38-3)

Ethyl 3-(1,3-dimethyl-2-imidazolio)propenimidate iodide hydrochloride was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.46 (3H, t, J=7Hz), 3.97 (6H, s), 4.58 (2H, q, J=7Hz), 7.39 (1H, d, J=16.5Hz), 7.82 (1H, d, J=16.5Hz), 7.95 (2H, s)

Preparation 39-1)

To a solution of 1-methyl-4-(hydroxymethyl)pyrazole (0.47 g) in dichloromethane (5.0 ml) was added dropwise thionyl chloride (0.31 ml) at -30° - -20°C. After adding

one drop of N,N-dimethylformamide, the mixture was allowed to warm to ambient temperature for 2 hours. Evaporation of the mixture gave 4-chloromethyl-1-methylpyrazole hydrochloride (0.65 g).

NMR (DMSO-d_6, δ) : 3.82 (3H, s), 4.69 (2H, s), 7.51 (1H, s), 7.82 (1H, s)

Preparation 39-2)

To a solution of sodium cyanide (6.88 g) in water was added by portions 4-chloromethyl-1-methylpyrazole obtained in Preparation 39-1) (11.7 g) at 0°C. After stirring at 0°C for 20 minutes, the reaction mixture was evaporated, and the residue was chromatographed on silica gel (300 ml) eluting with a mixture of dichloromethane and methanol (99.5:0.5 to 9:1, V/V) to give 4-cyanomethyl-1-methylpyrazole (3.31 g).

IR (Nujol) : 2250 cm^{-1}

NMR ($CDCl_3$, δ) : 3.58 (2H, s), 3.89 (3H, s), 7.39 (1H, s), 7.42 (1H, s)

Preparation 39-3)

To a solution of 4-cyanomethyl-1-methylpyrazole (3.27 g) in dichloromethane (15 ml) was added methyl trifluoromethanesulfonate (triflate) (3.2 ml) at 0°C. The mixture was allowed to warm to ambient temperature. After 4 hours' stirring at ambient temperature, the resulting oil was separated by decantation, washed with pentane, and dried in vacuo to give 4-cyanomethyl-1,2-dimethylpyrazolium trifluoromethanesulfonate which was used for the next step without further purification.

NMR (DMSO-d_6, δ) : 4.04 (2H, s), 4.08 (6H, s), 8.50 (2H, s)

Preparation 39-4)

Ethyl 2-(1,2-dimethyl-4-pyrazolio)acetimidate trifluoromethanesulfonate hydrochloride (10.16 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.21 (3H, t, J=7Hz), 3.71 (2H, s), 4.10 (6H, s), 4.14 (2H, q, J=7Hz), 8.39 (2H, s)

Preparation 40-1)

To a stirred solution of methylthioacetonitrile (2.5 ml) in dichloromethane (25 ml) was added methyl triflate (3.4 ml) at 0°C and the mixture was allowed to stand at ambient temperature for 7 days. Evaporation of the mixture gave dimethylsulfonioacetonitrile trifluoromethanesulfonate (7.53 g) which was used for the next step without further purification.

NMR (DMSO-d_6, δ) : 2.99 (6H, s), 4.75 (2H, s)

Preparation 40-2)

Ethyl 2-(dimethylsulfonio)acetimidate trifluoromethanesulfonate hydrochloride (8.45 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.26 (3H, t, J=7Hz), 2.98 (6H, s), 4.24 (2H, q, J=7Hz), 4.62 (2H, s)

Preparation 41

Ethyl 2-(N-allyloxycarbonyl-N-methylamino)acetimidate hydrochloride (39.5 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.33 (3H, t, J=6.8Hz), 2.8-3.1 (3H, m), 4.35-4.6 (4H, m), 5.1-5.4 (2H, m), 5.8-6.1 (1H, m)

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Preparation 42

To a stirred solution of N,N,-dimethylformamide (7.74 ml) in benzene (50 ml) was added dimethyl sulfate (9.03 ml) at ambient temperature. The resulting mixture was warmed to 40°C for 10 hours. Evaporation of the mixture gave methyl N,N-dimethyl-N-(methoxymethylene)iminium methanesulfonate.

NMR (DMSO-d_6, δ) : 3.12 (3H, s), 3.31 (3H, s), 3.40 (3H, s), 4.29 (3H, s)

Preparation 43

Ethyl 2-(N-allyloxycarbonylamino)acetimidate hydrochloride (497 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.34 (3H, t, J=6.8Hz), 4.15 (2H, d, J=5.7Hz), 4.4-4.6 (4H, m), 5.1-5.4 (2H, m), 5.8-6.1 (1H, m), 8.01 (1H, t, J=5.7Hz)

Preparation 44-1)

A mixture of 4-bromobutanenitrile (1.49 g) and N-methylpyrrolidine (1.25 ml) in benzene (5 ml) was heated to 70°C for 5 hours. After cooling, the resulting precipitate was collected by filtration, washed with diethyl ether and dried to give 4-(N-methyl-1-pyrrolidinio)butanenitrile (11.83 g).

NMR (DMSO-d_6, δ) : 1.8-2.4 (6H, m), 2.56 (2H, t, J=6Hz), 3.05 (3H, s), 3.35-3.7 (6H, m)

Preparation 44-2)

Ethyl 4-(N-methyl-1-pyrrolidinio)butanimidate bromide hydrochloride (17.28 g) was obtained in substantially the same manner as that of Preparation 1.

NMR (DMSO-d_6, δ) : 1.38 (3H, t, J=6.8Hz), 1.9-2.2 (6H, m), 3.05 (3H, s), 3.3-3.7 (6H, m), 4.48 (2H, q, J=6.8Hz)

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Example 1

A solution of (4R,5S,6S)-3-(azetidin-3-yl)thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (300 mg) in water (20 ml) and acetonitrile (20 ml) was cooled at 0°C and the pH was adjusted to around 8.5 with 10% aqueous sodium hydroxide. The solution was added ethyl carbamoylacetimidate hydrochloride (670 mg) at 0°C, while adjusting pH around 8.0 with 10% aqueous sodium hydroxide. After stirring for

(continued on the next page)

30 minutes at 0°C, the mixture was adjusted to around pH 7.0 with 1N aqueous hydrochloric acid. The mixture was washed with ethyl acetate and dichloromethane, and concentrated to an oil (about 10 ml). The obtained oil was chromatographed on Diaion HP-20 (Trademark, made by Mitsubishi Chemical Industries) (50 ml) eluting in turn with water (100 ml), and a mixture of water and acetonitrile (95:5) to give an oil. The oil was concentrated and chromatographed again with silica gel (40 ml). Eluting with a mixture of water and acetonitrile (1:3), and concentrating and freeze-drying of the eluate gave (4R,5S,6S)-3-[1-(2-carbamoylacetimidoyl)azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (153 mg).

IR (Nujol) : 1750 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.19 (3H, d, J=7.0Hz), 1.29 (3H, d, J=6.4Hz), 3.1-3.5 (2H, m), 4.0-4.2 (8H, m)

The following compounds were obtained in substantially the same manner as that of Example 1.

Example 2

(4R,5S,6S)-3-[1-{2-(1-Methyl-1H-tetrazol-5-ylthio)-acetimidoyl}azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.20 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.4Hz), 3.1-3.3 (1H, m), 3.46 (1H, dd, J=2.5Hz, J=6.2Hz), 4.07 (3H, s), 4.0-4.4 (5H, m)

Example 3

(4R,5S,6S)-3-[1-{2-(Methylthio)acetimidoyl}azetidin-

3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1750 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.20 (3H, d, J=7.14Hz), 1.30 (3H, d, J=6.2Hz), 2.19 (3H, s), 3.2-3.3 (1H, m), 3.45 (4H, br s), 4.2-4.4 (5H, m)

Example 4

(4R,5S,6S)-3-[1-(2-Methoxyacetimidoyl)azetidin-3-yl]-thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.19 (3H, d, J=7.12Hz), 1.30 (3H, d, J=6.4Hz), 3.1-3.3 (1H, m), 3.47 (4H, br s), 3.8-4.4 (6H, m)

Example 5

(4R,5S,6S)-3-[1-{2-(Acetylamino)acetimidoyl}azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1750 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.19 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.3Hz), 2.09 (3H, s), 3.2-3.5 (2H, m), 4.0-4.4 (9H, m)

Example 6

(4R,5S,6S)-3-[1-{2-(N,N-Dimethylcarbamoyl)-acetimidoyl}azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1750 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.19 (3H, d, J=7.1Hz), 1.30 (3H, d, J=6.3Hz), 2.98 (3H, s), 3.07 (3H, s), 3.0-3.3 (1H, m), 3.4-3.5 (1H, m), 4.0-4.4 (6H, m)

Example 7

(4R,5S,6S)-3-[1-{2-(3-Hydroxyazetidin-1-ylcarbonyl)-acetimidoyl}azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740 cm^{-1}

NMR (200MHz, D_2O, δ) : 1.19 (3H, d, J=7.0Hz), 1.30 (3H, d, J=4.5Hz), 3.1-3.5 (2H, m), 3.8-4.6 (6H, m)

Example 8

To a solution of (4R,5S,6S)-3-(azetidin-3-yl)thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (1.6 g) in a mixture of phosphate buffer (pH 6.86, 60 ml), tetrahydrofuran (30 ml) and water (60 ml) was added by portions ethyl 4-(N-carbamoylmethyl-N,N-dimethylammonio)butyrimidate bromide hydrochloride (1.8 g) while adjusting pH to around 8.5 with 30% aqueous potassium carbonate at 0°C. After stirring at pH 8.5 for another 30 minutes, the pH was adjusted to 7.0 with hydrochloric acid (6N) at 0°C. The reaction mixture was washed four times with a mixture of tetrahydrofuran and ethyl acetate (3:7 V/V, total 800 ml) and evaporated in vacuo to give a residual aqueous solution, which was chromatographed on Diaion HP-20 (150 ml) eluting with a mixture of water and acetonitrile (100:0 to 92:8, V/V). The objective fractions were collected, lyophilized to give an amorphous, which was further chromatographed on γ-alumina eluting with water. The objective fractions were collected, passed through Amberlyst A-26 (Cl^- form, Trademark, made by Rohm & Haas Co.) (30 ml). Lyophilization of the eluate gave (4R,5S,6S)-3-[1-{4-(N-carbamoylmethyl-N,N-dimethyl-ammonio)butyrimidoyl}azetidin-3-ylthio]-6-[(1R)-1-

hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride (495 mg).

IR (Nujol) : 3250, 1740, 1680, 1630, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.4Hz), 2.01-2.25 (2H, m), 2.40-2.61 (2H, m), 3.10-3.30 (1H, m), 3.31 (6H, s), 3.46 (1H, dd, J=2.5Hz, J=6.1Hz), 3.60-3.80 (2H, m), 4.10-4.40 (7H, m), 4.62-5.00 (2H, m)

The following compounds were obtained in substantially the same manner as that of Example 15-1).

Example 9-1)

(4R,5S,6S)-3-[1-[2-(Allyloxycarbonylamino)-acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

NMR (D_2O, δ) : 1.18 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.1-3.3 (1H, m), 3.45 (1H, dd, J=3Hz, 6Hz), 4.09 (2H, d, J=3Hz), 4.15-4.55 (5H, m), 4.55-5.0 (4H, m), 5.2-5.45 (2H, m), 5.8-6.1 (1H, m)

Example 9-2)

(4R,5S,6S)-3-[1-[2-(N-Allyloxycarbonyl-N-methylamino)acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.98, 3.20 (total 3H, each s), 3.1-3.4 (1H, m), 3.44 (1H, dd, J=3Hz, 6Hz), 4.1-4.5 (7H, m), 4.63, 4.66 (total 2H, each s), 4.68-5.0 (2H, m), 5.2-5.45 (2H, m), 5.8-6.1 (1H, m)

Example 9-3)

(4R,5S,6S)-3-[1-[2-[N-Allyloxycarbonyl-N-(carbamoylmethyl)amino]acetimidoyl]azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740, 1700, 1680, 1575 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7.12Hz), 1.30 (3H, d, J=6.35Hz), 3.10-3.35 (1H, m), 3.45 (1H, dd, J=6.14Hz, 2.44Hz), 4.17-4.40 (9H, m), 4.60-4.80 (4H, m), 5.20-5.40 (2H, m), 5.80-6.15 (1H, m)

Example 9-4)

(4R,5S,6S)-3-[1-[2-[N-[2-(Allyloxycarbonyloxy)-ethyl]-N-allyloxycarbonylamino]acetimidoylazetidin-3-yl]-thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1735, 1680 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.2Hz), 1.28 (3H, d, J=6.3Hz), 3.10-3.30 (1H, m), 3.45 (1H, dd, J=6.1Hz, 2.5Hz), 3.70 (2H, br s), 4.10-4.40 (9H, m), 4.60-4.80 (6H, m), 5.20-5.40 (4H, m), 5.80-6.15 (2H, m)

Example 10-1)

To a solution of (4R,5S,6S)-3-[1-[2-(allyloxycarbonylamino)acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (1.04 g) in a mixture of phosphate buffer (pH 6.86, 2.5 ml) and ethanol (6 ml) were added successively tri-n-butyltin hydride (0.96 ml), acetic acid (0.21 ml) and a solution of triphenylphosphine (0.12 g) and tetrakis(triphenylphosphine)palladium (0.21 g) in tetrahydrofuran (12 ml) under vigorous stirring at ambient temperature. Stirring was continued for 10 minutes and to the mixture was added a mixture of cold water (100 ml), dichloromethane (100 ml) and sodium

chloride (2 g). The aqueous layer was separated, washed twice with dichloromethane, and evaporated in vacuo. The residue was chromatographed on Diaion HP-20 (200 ml) eluting with a mixture of water and acetonitrile (100:0 to 90:10, V/V). The objective fractions were collected, and lyophilized to give an amorphous (0.40 g). One forth of this sample (100 mg) was further chromatographed on silica gel (10 ml) eluting with a mixture of acetonitrile and water (100:0 to 70:30, V/V). The objective fractions were collected, concentrated in vacuo, and passed through Amberlyst A-26 (Cl^- form, 2 ml). Lyophilization of the eluate gave (4R,5S,6S)-3-[1-(2-aminoacetimidoyl)azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride (85 mg).

IR (Nujol) : 3250, 1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.1-3.3 (1H, m), 3.44 (1H, dd, J=3, 6Hz), 3.54 (2H, d, J=3.5Hz), 4.0-4.5 (5H, m), 4.6-5.0 (2H, m)

The following compounds were obtained in substantially the same manner as that of Example 10-1).

Example 10-2)

(4R,5S,6S)-3-[1-[2-(Methylamino)acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride

IR (Nujol) : 3300, 1740, 1670, 1570 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.2Hz), 1.29 (3H, d, J=6.3Hz), 2.49 (3H, s), 3.1-3.35 (1H, m), 3.45 (1H, dd, J=6.1, 2.5Hz), 3.61, 3.62 (total 2H, each s), 4.1-4.5 (5H, m), 4.6-5.0 (2H, m)

Example 10-3)

(4R,5S,6S)-3-[1-[2-(Carbamoylmethylamino)-acetimidoyl]azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1735 cm^{-1}

NMR (D_2O, δ) : 1.17 (3H, d, J=7.14Hz), 1.28 (3H, d, J=6.32Hz), 3.10-3.30 (1H, m), 3.39 (2H, s), 3.43 (1H, dd, J=6.20Hz, 2.40Hz), 3.56 (2H, d, J=3.18Hz), 4.20-4.40 (5H, m), 4.30-4.80 (2H, m)

Example 10-4)

(4R,5S,6S)-3-[1-[2-[(2-Hydroxyethyl)amino]-acetimidoyl]azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740, 1680 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.1Hz), 1.28 (3H, d, J=6.3Hz), 2.99 (2H, t, J=4.9Hz), 3.10-3.35 (1H, m), 3.43 (1H, dd, J=6.2Hz, 2.4Hz), 3.70-3.80 (4H, m), 4.20-4.45 (5H, m)

The following compounds were obtained in substantially the same manner as that of Example 15-1).

Example 11-1)

(4R,5S,6S)-3-[1-[3-[N-Allyloxycarbonyl-N-(carbamoylmethyl)amino]propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid

NMR (D_2O, δ) : 1.17 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.5-2.7 (2H, m), 3.0-3.4 (1H, m), 3.45 (1H, dd, J=3, 6Hz), 3.5-3.95 (3H, m), 4.0-4.6 (6H, m), 4.6-5.0 (4H, m), 5.2-5.55 (2H, m), 5.6-6.2 (1H, m)

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Example 11-2)

(4R,5S,6S)-3-[1-[2-[N-[4-(Allyloxycarbonylamino)-butyl]carbamoyl]acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3200, 1740, 1640, 1570 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.4-1.7 (4H, m), 3.0-3.4 (5H, m), 3.45 (1H, dd, J=3, 6Hz), 4.05-4.4 (5H, m), 4.5-4.65 (2H, m), 4.65-5.0 (2H, m), 5.15-5.4 (2H, m), 5.8-6.05 (1H, m)

Example 11-3)

(4R,5S,6S)-3-[1-[2-[4-[5-(Allyloxycarbonylamino)-pentanoyl]piperazin-1-ylcarbonyl]acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3200, 1740, 1680, 1620 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.4-1.8 (4H, m), 2.4-2.55 (2H, m), 3.05-3.4 (3H, m), 3.44 (1H, dd, J=3Hz, 6Hz), 3.50-3.80 (8H, m), 4.0-4.5 (5H, m), 4.56 (2H, d, J=5Hz), 4.65-4.95 (2H, m), 5.15-5.4 (2H, m), 5.8-6.0 (1H, m)

Example 12-1)

To a solution of (4R,5S,6S)-3-[1-[3-[N-allyloxycarbonyl-N-(carbamoylmethyl)amino]propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (2.24 g) in a mixture of phosphate buffer (pH 6.86, 5.6 ml) and ethanol (13.5 ml) were added successively tri-n-butyltin hydride (1.7 ml), acetic acid (0.36 ml) and a solution of triphenylphosphine (0.21 g) and tetrakis(triphenylphosphine)palladium (0.37 g) in

tetrahydrofuran (27 ml) under vigorous stirring at ambient temperature. Stirring was continued for 10 minutes and to the mixture was added a mixture of cold water (100 ml) and ethyl acetate (200 ml). The aqueous layer was separated, washed twice with ethyl acetate and concentrated in vacuo. The residue was chromatographed on Diaion HP-20 (300 ml) eluting with a mixture of water and acetonitrile (100:0 to 94:6, V/V). The objective fractions were collected, and lyophilized to give an amorphous, which was further chromatographed on Alumina AC-12 (made by Sumitomo Chemical Co., Ltd.) (370 ml) eluting with water. The objective fractions were collected, concentrated and passed through Amberlyst A-26 (Cl^- form, 5 ml). Lyophilization of the eluate gave (4R,5S,6S)-3-[1-[3-(carbamoylmethylamino)propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid (837 mg).

IR (Nujol) : 3300, 1730, 1670, 1620 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.8-3.0 (2H, m), 3.1-3.35 (1H, m), 3.35-3.5 (3H, m), 3.97 (2H, s), 4.0-4.5 (5H, m), 4.6-4.9 (2H, m)

After the usual chromatographic purification of (4R,5S,6S)-3-[1-[3-(carbamoylmethylamino)propanimidoyl]-azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid by 7-alumina eluting with water, the column was washed throughly with aqueous sodium chloride (5%). The washings were evaporated in vacuo, and the residue was chromatographed on Diaion HP-20 (50 ml) eluting with a mixture of water and acetonitrile (0:100 to 15:85, V/V). Lyophilization of the eluate gave (4R,5S,6S)-3-(1-allylazetidin-3-ylthio)-6-[(1R)-1-hydroxyethyl]-4-methyl-

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7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (60 mg) as a by-product.

IR (Nujol) : 3250, 1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.16 (3H, d, J=7.2Hz), 1.29 (3H, d, J=6.3Hz), 3.1-3.3 (1H, m), 3.45 (1H, dd, J=2.6Hz, 6.1Hz), 3.85 (2H, d, J=6.5Hz), 4.0-4.4 (5H, m), 4.4-4.55 (2H, m), 5.4-5.6 (2H, m), 5.7-5.9 (1H, m)

Example 12-2)

(4R,5S,6S)-3-[1-[2-[N-(4-Aminobutyl)carbamoyl]-acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride (1.25 g) was obtained in substantially the same manner as that of the former part of Example 12-1).

IR (Nujol) : 3200, 1740, 1650, 1560 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.4-1.8 (4H, m), 3.02 (2H, t, J=6Hz), 3.1-3.4 (3H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 4.1-4.4 (5H, m), 4.6-4.95 (2H, m)

Example 12-3)

(4R,5S,6S)-3-[1-[2-[4-(5-Aminopentanoyl)piperazin-1-ylcarbonyl]acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride (1.92 g) was obtained in substantially the same manner as that of former part of Example 12-1).

IR (Nujol) : 3250, 1730, 1620 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 1.5-1.85 (4H, m), 2.54 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 3.1-3.4 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.5-3.8 (8H, m), 4.1-4.45 (5H, m), 4.7-4.9 (2H, m)

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Example 13-1)

To a solution of (4R,5S,6S)-3-(azetidin-3-ylthio)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (4.0 g) in a mixture of phosphate buffer (pH 6.86, 120 ml) and tetrahydrofuran (30 ml) was added ethyl 3-(p-nitrobenzyloxycarbonylamino)-propanimidate hydrochloride (4.45 g) while adjusting pH to around 8.5 with 30% aqueous potassium carbonate at 0°C. After stirring at pH 8.5 for another 30 minutes, pH was adjusted to 7.0 with hydrochloric acid (6N) at 0°C. The reaction mixture was washed with a mixture of tetrahydrofuran and ethyl acetate (3:7 V/V, total 500 ml). The resulting solution containing (4R,5S,6S)-3-[1-[3-(4-nitrobenzyloxycarbonylamino)propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride (0.56 g) was used for the next step without further purification, because the object product was unstable under chromatographic conditions.

Example 13-2)

To a solution of (4R,5S,6S)-3-[1-[3-(4-nitrobenzyloxycarbonylamino)propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride obtained in Example 13-1) were added sodium hydrogen phosphate dodecahydrate (1.2 g), sodium dihydrogen phosphate dihydrate (0.2 g) and palladium hydroxide (20% on carbon, 0.5 g), and the resulting mixture was stirred vigorously under atmospheric pressure of hydrogen at ambient temperature for 3 hours. The catalyst was removed by filtration and the filtrate was washed three times with ethyl acetate. Concentration in vacuo gave an aqueous residue which was chromatographed on Diaion HP-20 (200 ml)

eluting with a mixture of water and acetonitrile (100:0 to 92:8, V/V). Lyophilization gave an amorphous which was further chromatographed on alumina AC-12 (200 ml) eluting with water. The objective fractions were collected, concentration in vacuo, and passed through Amberlyst A-26 (Cl^- form, 20 ml). Lyophilization of the eluate gave (4R,5S,6S)-3-[1-(3-aminopropanimidoyl)azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride (0.56 g).

IR (Nujol) : 3300, 1745, 1680, 1640, 1575 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.7-2.9 (2H, m), 3.1-3.4 (3H, m), 3.47 (1H, dd, J=3Hz, 6Hz), 4.1-4.5 (5H, m), 4.6-5.0 (2H, m)

The following compounds were obtained in substantially the same manner as that of Example 15-1).

Example 14-1)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[N-(1,3,4-thiadiazol-2-yl)formimidoyl]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740, 1720, 1602 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.3Hz), 3.15-3.38 (1H, m), 3.38-3.50 (1H, m), 4.05-4.45 (5H, m), 4.58-4.80 (2H, m), 8.14 (1H, s), 8.91 (1H, s)

Example 14-2)

(4R,5S,6S)-3-[1-(N-Methylformimidoyl)azetidin-3-yl]-thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1750, 1700, 1590 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.2Hz), 1.29 (3H, d,

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J=6.1Hz), 2.90, 3.06, 3.18 (total 3H, s), 3.10-3.30 (1H, m), 3.40-3.50 (1H, m), 3.85-4.50 (7H, m), 4.55-4.80 (2H, m), 7.73, 7.76 (total 1H, s)

Example 14-3)

(4R,5S,6S)-3-[1-(N,N-Dimethyliminiomethyl)azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate from (4R,5S,6S)-3-(azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid and N,N-dimethyl-N-(methoxymethylene)-iminium methanesulfonate.

IR (Nujol) : 1745, 1690, 1598 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.2Hz), 1.29 (3H, d, J=6.3Hz), 3.05-3.35 (1H, m), 3.11, 3.18 (total 6H, both s), 3.40-3.50 (1H, m), 3.85-4.50 (5H, m), 4.60-4.85 (2H, m), 7.57 (1H, s)

Example 14-4)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[1-methyl-2-(1-pyrrolinio)]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (Nujol) : 1758, 1678, 1603 cm^{-1}

NMR (D_2O, δ) : 1.18 (3H, d, J=7.2Hz), 1.29 (3H, d, J=6.3Hz), 1.85-2.10 (1H, m), 2.32 (1H, dt, J=86.3Hz, 7.2Hz), 2.65-2.90 (2H, m), 3.05-3.30 (1H, m), 3.10 (3H, s), 3.35-3.50 (1H, m), 3.65-3.80 (2H, m), 4.00-4.45 (5H, m), 4.60-4.85 (2H, m)

Example 15-1)

To a solution of (4R,5S,6S)-3-(azetidin-3-ylthio)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-

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hept-2-ene-2-carboxylic acid (0.4 g) in a mixture of phosphate buffer (pH 6.86, 80 ml) and tetrahydrofuran (20 ml) was added by portions ethyl 2-(difluoromethylthio)-acetimidate hydrochloride (0.55 g) while adjusting pH to around 8.5 with 30% aqueous potassium carbonate at 0°C. After stirring at pH 8.5 for another 30 minutes, pH was adjusted to 7.0 with hydrochloric acid (6N) at 0°C. The reaction mixture was washed four times with a mixture of tetrahydrofuran and ethyl acetate (3:7 V/V, total 40 ml) and evaporated in vacuo to give a residual aqueous solution, which was chromatographed on Diaion HP-20 (50 ml) eluting with a mixture of water and acetonitrile (100:0 to 90:10, V/V).

The objective fractions were collected and lyophilized to give an amorphous, which was further chromatographed on silica gel (20 ml) eluting with a mixture of acetonitrile and water (100:0 to 70:30, V/V). Lyophilization of the eluate gave (4R,5S,6S)-3-[1-[2-(difluoromethylthio)acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (0.20 g).

IR (Nujol) : 3300, 1740, 1670, 1630, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.1-3.3 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 4.1-4.6 (5H, m), 4.6-5.1 (2H, m), 7.15 (1H, t, J=55Hz)

The following compounds were obtained in substantially the same manner as that of Example 15-1).

Example 15-2)

(4R,5S,6S)-3-[1-[2-(Carbamoyloxy)acetoimidoyl]-azetidin-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1730, 1670, 1580 cm^{-1}

NSDOCID: <WO 9323402A1 >

NMR (D_2O, δ) : 1.24 (3H, d, J=7.2Hz), 1.29 (3H, d, J=6.1Hz), 3.06-3.33 (1H, m), 3.33-3.53 (1H, m), 3.96-4.50 (7H, m), 4.50-4.83 (2H, m)

Example 15-3)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(methoxyacetylamino)acetimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1750, 1670, 1590 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7.1Hz), 1.30 (3H, d, J=6.3Hz), 3.05-3.35 (1H, m), 3.35-3.55 (1H, m), 3.46 (3H, s), 4.10 (2H, s), 4.15-4.50 (7H, m), 4.60-4.80 (2H, m)

Example 15-4)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[2-(pyridin-3-yl)acetimidoyl]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3200, 1745, 1590 cm^{-1}

NMR (D_2O, δ) : 1.16 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.05-3.3 (1H, m), 3.44 (1H, d, J=3.6Hz), 3.88, 3.89 (total 2H, each s), 4.0-4.4 (5H, m), 4.6-5.0 (2H, m), 7.4-7.55 (1H, m), 7.83 (1H, d, J=8Hz), 8.4-8.6 (2H, m)

Example 15-5)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[2-(1-methyl-3-pyridinio)acetimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.1-3.3 (1H, m), 3.4-3.5 (1H, m), 4.1-4.5 (10H, m), 4.6-4.9 (2H, m), 7.95-8.2 (1H, m), 8.45-8.54 (1H, m), 8.7-8.9 (2H, m)

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Example 15-6)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[3-(pyridin-3-yl)propanimidoyl]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1740, 1670, 1620 cm-1

NMR (D_2O, δ) : 1.13 (3H, d, J=7.1Hz), 1.28 (3H, d, J=6.3Hz), 2.60-2.90 (2H, m), 2.90-3.35 (3H, m), 3.35-3.50 (1H, m), 3.80-4.40 (5H, m), 4.50-4.75 (2H, m), 7.65-7.85 (1H, m), 8.05-8.20 (1H, m), 8.45-8.75 (2H, m)

Example 15-7)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[3-(1-methyl-3-pyridinio)propanimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1580 cm-1

NMR (D_2O, δ) : 1.17 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.6-2.9 (2H, m), 3.0-3.4 (3H, m), 3.4-3.5 (1H, m), 4.0-4.4 (5H, m), 4.6-5.0 (2H, m), 8.0-8.1 (1H, m), 8.48 (1H, d, J=8Hz), 8.6-8.8 (1H, m), 8.79 (1H, s)

Example 15-8)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[3-(pyridin-3-yl)propenimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.2-3.4 (1H, m), 3.45 (1H, dd, J=3Hz, 6Hz), 4.0-4.5 (5H, m), 4.6-4.9 (2H, m), 6.67 (1H, d, J=16Hz), 7.5-7.7 (2H, m), 8.05-8.2 (1H, m), 8.55-8.75 (2H, m)

Example 15-9)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[3-(1-methyl-3-pyridinio)propenimidoyl]azetidin-3-ylthio]-7-

oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1660, 1580 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.1-3.4 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 4.44 (3H, s), 4.2-4.6 (5H, m), 4.6-5.1 (2H, m), 6.94 (1H, dd, J=16Hz, 5Hz), 7.65 (1H, d, J=16Hz), 8.11 (1H, t, J=7Hz), 8.73-8.86 (2H, m), 9.11 (1H, m)

Example 15-10)

(4R,5S,6S)-3-[1-[3-(1-Carbamoylmethyl-3-pyridinio)-propenimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1680 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.1-3.35 (1H, m), 3.45 (1H, dd, J=2.5Hz, 6Hz), 4.20-4.52 (5H, m), 4.80-5.0 (2H, m), 6.95 (1H, d, J=16.5Hz), 7.70 (1H, d, J=16.5Hz), 8.19 (1H, dd, J=6Hz, 8Hz), 8.84-8.89 (2H, m), 9.16 (1H, d, J=7Hz)

Example 15-11)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[4-(1-pyridinio)butyrimidoyl]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1570 cm^{-1}

NMR (D_2O, δ) : 1.16 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.2-2.8 (4H, m), 3.1-3.4 (1H, m), 3.4-3.5 (1H, m), 3.9-4.4 (5H, m), 4.4-5.0 (2H, m), 8.13 (2H, t, J=7Hz), 8.16 (1H, t, J=7Hz), 8.89 (2H, d, J=7Hz)

Example 15-12)

INSDOCID: <WO__9323402A1_I_>

(4R,5S,6S)-3-[1-[2-[N-[2-[N-(2-Hydroxyethyl)-N,N-dimethylammonio]ethyl]carbamoyl]acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1650, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.22 (6H, s), 3.05-3.25 (1H, m), 3.47 (1H, dd, J=3Hz, 6Hz), 3.5-3.6 (4H, m), 3.65-3.8 (2H, m), 4.0-4.1 (2H, m), 4.1-4.4 (5H, m), 4.6-4.9 (2H, m)

Example 15-13)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[2-(trifluoroacetylamino)acetimidoyl]azetidin-3-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1735, 1700, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 1.18 (3H, d, J=7.18Hz), 1.28 (3H, d, J=6.35Hz), 3.15-3.35 (1H, m), 3.45 (1H, dd, J=6.12Hz, 2.50Hz), 4.19-4.45 (7H, m), 4.60-5.00 (2H, m)

Example 15-14)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(methoxycarbonylamino)acetimidoyl]azetidin-3-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1735, 1720, 1680 cm^{-1}

NMR (D_2O, δ) : 1.24 (3H, d, J=7.19Hz), 1.28 (3H, d, J=6.34Hz), 3.15-3.35 (1H, m), 3.45 (1H, dd, J=6.09Hz, 2.50Hz), 3.70 (3H, s), 4.07 (2H, d, J=3.65Hz), 4.20-4.45 (5H, m), 4.60-5.00 (2H, m)

Example 15-15)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(methanesulfonylamino)acetimidoyl]azetidin-3-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

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IR (Nujol) : 1730, 1670, 1580 cm-1

NMR (D_2O, δ) : 1.18 (3H, d, J=7.19Hz), 1.28 (3H, d, J=6.35Hz), 3.15 (3H, s), 3.10-3.30 (1H, m), 3.44 (1H, dd, J=6.12Hz, 2.50Hz), 4.12 (2H, d, J=2.52Hz), 4.20-4.45 (5H, m), 4.60-5.00 (2H, m)

Example 15-16)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-(2-ureidoacetimidoyl)azetidin-3-ylthio]-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1742, 1665, 1582 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.3Hz), 3.10-3.37 (1H, m), 3.39-3.50 (1H, m), 3.85-4.50 (5H, m), 4.04 (2H, d, J=3.2Hz), 4.60-4.90 (2H, m)

Example 15-17)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-(imidazol-1-yl)butyrimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3300, 1735, 1620, 1580 cm-1

NMR (D_2O, δ) : 1.18 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.0-2.3 (2H, m), 2.3-2.5 (2H, m), 3.1-3.3 (1H, m), 3.44 (1H, dd, J=2.5Hz, 6Hz), 3.9-4.4 (7H, m), 4.5-4.9 (2H, m), 7.09 (1H, s), 7.22-7.25 (1H, m), 7.77 (1H, s)

Example 15-18)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[4-(3-methyl-1-imidazolio)butyrimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3350, 1750, 1705 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d,

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J=6Hz), 2.1-2.4 (2H, m), 2.4-2.6 (2H, m), 3.1-3.3 (1H, m), 3.47 (1H, dd, J=3, 6Hz), 3.92 (3H, s), 4.0-4.4 (7H, m), 4.6-4.9 (2H, m), 7.50 (1H, s), 7.54 (1H, s), 8.81 (1H, s)

Example 15-19)

(4R,5S,6S)-3-[1-[4-(2-Methylimidazol-1-yl)-butyrimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 1743, 1677, 1578

NMR (D_2O, δ) : 1.19 (3H, d, J=7.2Hz), 1.30 (3H, d, J=6.4Hz), 2.10-2.30 (2H, m), 2.40-2.55 (2H, m), 2.61-2.62 (total 3H, s), 3.10-3.30 (1H, m), 3.40-3.50 (1H, m), 4.00-4.40 (5H, m), 4.50-4.80 (2H, m)

Example 15-20)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-(4-hydroxymethyl-1-methyl-3-imidazolio)butyrimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3200, 1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.1-2.3 (2H, m), 2.4-2.6 (2H, m), 3.1-3.3 (1H, m), 3.47 (1H, dd, J=3, 6Hz), 3.89 (3H, s), 4.0-4.4 (7H, m), 4.6-5.0 (2H, m), 7.49 (1H, s), 8.83 (1H, s)

Example 15-21)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-[3-(2-hydroxyethyl)-1-imidazolio]butyrimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730, 1670, 1620, 1570 cm^{-1}

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NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.1-2.4 (2H, m), 2.4-2.6 (2H, m), 3.1-3.4 (1H, m), 3.46 (1H, dd, J=3, 6Hz), 3.90-3.98 (2H, m), 4.0-4.5 (9H, m), 4.6-4.9 (2H, m)

Example 15-22)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[1-[4-(3-thiazolio)butyrimidoyl]azetidin-3-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1680 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.2-2.6 (4H, m), 3.1-3.3 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 4.0-4.4 (7H, m), 4.55-4.9 (2H, m), 8.20-8.28 (1H, m), 8.38-8.45 (1H, m)

Example 15-23)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[6-(3-methyl-1-imidazolio)hexanimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1745, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.25-1.45 (2H, m), 1.5-1.7 (2H, m), 1.7-2.1 (2H, m), 2.3-2.45 (2H, m), 3.0-3.3 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.90 (3H, s), 4.0-4.4 (7H, m), 4.5-4.8 (2H, m), 7.4-7.5 (2H, m), 8.73 (1H, s)

Example 15-24)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(imidazol-4-yl)acetimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

NMR (D_2O, δ) : 1.17 (3H, d, J=7Hz), 1.29 (3H, d,

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J=6Hz), 3.05-3.30 (1H, m), 3.43 (1H, dd, J=3Hz, 6Hz), 3.77 (2H, d, J=3Hz), 4.1-4.4 (5H, m), 4.6-4.9 (2H, m), 7.18 (1H, s), 7.77 (1H, d, J=1Hz)

Example 15-25)

(4R,5S,6S)-3-[1-[3-(Imidazol-4-yl)propanimidoyl]-azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3150, 1730, 1570 cm-1

NMR (D_2O, δ) : 1.15 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.5-2.8 (2H, m), 2.9-3.3 (3H, m), 3.4-3.5 (1H, m), 3.5-3.75 (1H, m), 3.9-4.4 (4H, m), 4.5-4.9 (2H, m), 7.03 (1H, s), 7.74 (1H, d, J=17Hz)

Example 15-26)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(3-methyl-1-imidazolio)acetimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730, 1640 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.05-3.4 (1H, m), 3.4-3.5 (1H, m), 3.93 (3H, s), 3.9-4.1 (1H, m), 4.1-4.4 (4H, m), 4.4-4.8 (2H, m), 5.05 (2H, d, J=4Hz), 7.46 (2H, d, J=8Hz), 8.76 (1H, s)

Example 15-27)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(1,3-dimethyl-2-imidazolio)acetimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1725, 1570 cm-1

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d,

J=6Hz), 3.1-3.3 (1H, m), 3.47 (1H, dd, J=3Hz, 6Hz), 3.88 (6H, s), 4.1-4.5 (5H, m), 4.8-5.05 (2H, m), 7.58 (2H, s)

Example 15-28)

(4R,5S,6S)-3-[1-[3-(1,3-Dimethyl-2-imidazolio)-propenimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 3.1-3.4 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.94 (6H, s), 4.1-4.6 (5H, m), 4.7-5.1 (2H, m), 6.85 (1H, dd, J=17Hz, 4Hz), 7.51 (1H, d, J=17Hz), 7.60 (2H, s)

Example 15-29)

(4R,5S,6S)-3-[1-[2-(1,3-Dimethyl-4-imidazolio)-acetimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730, 1560 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.05-3.4 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.81 (3H, s), 3.89 (3H, s), 4.02 (2H, d, J=4Hz), 4.15-4.5 (5H, m), 4.8-5.0 (2H, m), 7.57 (1H, s), 8.80 (1H, s)

Example 15-30)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[2-(1,2-dimethyl-4-pyrazolio)acetimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1720, 1570 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d,

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J=6Hz), 3.1-3.3 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.79, 3.80 (total 2H, each s), 4.12 (6H, s), 4.1-4.4 (5H, m), 4.6-4.95 (1H, m), 8.26, 8.27 (total 2H, each s)

Example 15-31)

(4R,5S,6S)-3-[1-[3-[N-(2-Hydroxyethyl)-N-methylamino]propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride

IR (Nujol) : 3300, 1740, 1580 cm-1

NMR (D_2O, δ) : 1.17 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.73 (3H, s), 2.70-2.9 (2H, m), 3.10 (2H, t, J=5.5Hz), 3.15-3.40 (3H, m), 3.45 (1H, dd, J=3Hz, 6Hz), 3.86 (2H, t, J=5.5Hz), 4.05-4.45 (5H, m), 4.5-4.9 (2H, m)

Example 15-32)

(4R,5S,6S)-3-[1-[3-(N-Carbamoylmethyl-N-methylamino)-propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride

IR (Nujol) : 3150, 1740, 1650, 1570 cm-1

NMR (D_2O, δ) : 1.20 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.33 (3H, s), 2.5-2.65 (2H, m), 2.7-2.9 (2H, m), 3.20 (2H, s), 3.15-3.4 (1H, m), 3.45 (1H, dd, J=3Hz, 6Hz), 4.05-4.4 (5H, m), 4.6-4.9 (2H, m)

Example 15-33)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-[N-(2-hydroxyethyl)carbamoylmethyl-N,N-dimethylammonio]-butyrimidoyl]azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1740, 1570 cm-1

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NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=7Hz), 2.0-2.35 (2H, m), 2.4-2.6 (2H, m), 3.29 (6H, s), 3.1-3.4 (1H, m), 3.4-3.6 (3H, m), 4.13 (2H, d, J=3Hz), 4.2-4.45 (5H, m), 4.6-5.0 (2H, m)

Example 15-34)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-[N-(2-hydroxyethyl)-N,N-dimethylammonio]butyrimidoyl]-azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3200, 1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.0-2.3 (2H, m), 2.4-2.6 (2H, m), 3.19 (6H, s), 3.05-3.15 (1H, m), 3.4-3.6 (5H, m), 4.0-4.4 (7H, m), 4.6-4.9 (2H, m)

Example 15-35)

(4R,5S,6S)-3-[1-[4-[N-(2-Carbamoyloxyethyl)-N,N-dimethylammonio]butyrimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730, 1570 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.0-2.3 (2H, m), 2.4-2.6 (2H, m), 3.20 (6H, s), 3.1-3.3 (1H, m), 3.4-3.6 (3H, m), 3.65-3.8 (2H, m), 4.0-4.45 (5H, m), 4.45-4.65 (2H, m), 4.65-4.9 (2H, m)

Example 15-36)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[1-[4-[N-(N-methylcarbamoylmethyl)-N,N-dimethylammonio]butyrimidoyl]-azetidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 1320, 1730, 1660, 1580 cm^{-1}

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NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.0-2.3 (2H, m), 2.4-2.6 (2H, m), 2.81 (3H, s), 3.28 (3H, s), 3.29 (3H, s), 3.15-3.40 (1H, m), 3.46 (1H, dd, J=3Hz, 6Hz), 3.5-3.75 (2H, m), 4.09 (2H, s), 4.15-4.40 (5H, m), 4.6-4.9 (2H, m)

Example 15-37)

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3-[1-[4-(1-methyl-1-pyrrolidinio)butyrimidoyl]azetidin-3-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3300, 1730, 1680 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.0-2.4 (6H, m), 2.4-2.6 (2H, m), 3.08 (3H, s), 3.1-3.15 (1H, m), 3.15-3.65 (9H, m), 4.0-4.4 (4H, m), 4.6-5.0 (2H, m)

Example 15-38)

(4R,5S,6S)-3-[1-[3-(2-Hydroxyethylamino)-propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride

IR (Nujol) : 3200, 1740, 1570 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.7-2.9 (2H, m), 3.1-3.3 (3H, m), 3.3-3.6 (3H, m), 3.86 (2H, t, J=6Hz), 4.1-4.5 (5H, m), 4.6-5.1 (2H, m)

Example 15-39)

(4R,5S,6S)-3-[1-[3-(Carbamoylmethylamino)-propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrochloride

IR (Nujol) : 3300, 1730, 1670, 1620 cm^{-1}

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NMR (D_2O, δ) : 1.18 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 2.8-3.0 (2H, m), 3.1-3.35 (1H, m), 3.35-3.5 (3H, m), 3.97 (2H, s), 4.0-4.5 (5H, m), 4.6-4.9 (2H, m)

Example 15-40)

(4R,5S,6S)-3-[1-[3-(Benzyloxycarbonylamino)-propanimidoyl]azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (Nujol) : 3200, 1745, 1690, 1585 cm^{-1}

NMR (D_2O, δ) : 1.17 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 2.4-2.6 (2H, m), 2.95-3.25 (1H, m), 3.35-3.65 (3H, m), 3.8-4.8 (7H, m), 5.14 (2H, s), 7.46 (5H, s)

Example 16

(4R,5S,6S)-3-[1-[2-(Dimethylsulfonio)acetimidoyl]-azetidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride

IR (Nujol) : 3250, 1730, 1670, 1570 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 3.17 (6H, s), 3.1-3.3 (1H, m), 3.47 (1H, dd, J=3, 6Hz), 4.1-4.6 (5H, m), 4.6-5.1 (2H, m)

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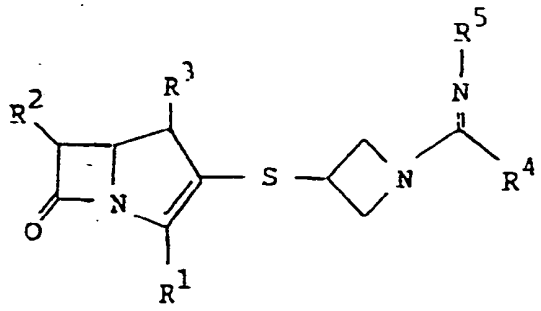
CLAIM

1. A compound of the formula :



in which R^1 is carboxy, COO^- or protected carboxy,
R^2 is hydroxy(lower)alkyl or protected hydroxy(lower)alkyl,
R^3 is hydrogen or lower alkyl, and
R^4 is substituted lower alkyl or substituted lower alkenyl and R^5 is hydrogen, or
R^4 is hydrogen and R^5 is heterocyclic group or lower alkyl or
R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkylimino, or
R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group,
or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein
R^4 is lower alkyl or lower alkenyl, each of which is substituted by the group consisting of carbamoyl,
N-(or N,N-di)(lower)alkylcarbamoyl,
N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino-(lower)alkyl]carbamoyl,
N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkyl-ammonio(lower)alkyl]carbamoyl,

N-[amino(or protected amino)(lower)alkyl]carbamoyl,
optionally substituted heterocyclic-thio,
lower alkylthio, di(lower)alkylsulfonio,
halo(lower)alkylthio,
lower alkoxy,
carbamoyloxy,
acylamino,
amino, protected amino,
lower alkylamino,
N-protected-N-(lower)alkylamino,
carbamoyl(lower)alkylamino,
N-protected-N-[carbamoyl(lower)alkyl]amino,
N-carbamoyl(lower)alkyl-N-(lower)alkylamino,
N-carbamoyl(lower)alkyl-N,N-di(lower)alkylammonio,
N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)-
alkylamino,
N-(lower alkylcarbamoyl)(lower)alkyl-N,N-
di(lower)alkylammonio,
optionally substituted heterocyclic-carbonyl,
optionally substituted
heterocyclic group,
[hydroxy(lower)alkyl]amino,
N-protected-N-[protected hydroxy(lower)alkyl]amino,
N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino,
N,N-di(lower)alkyl-N-[hydroxy(lower)alkyl]ammonio,
N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-
carbamoyl(lower)alkyl]amino,
N,N-di(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-
carbamoyl(lower)alkyl]ammonio,
N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino, or
N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-
ammonio, and R^5 is hydrogen, or

R^4 is hydrogen and R^5 is optionally substituted
hetrocyclic group or
lower alkyl, or

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R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkyliminio, or

R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group.

3. The compound of Claim 2, wherein

R^4 is carbamoyl(lower)alkyl,
N-(or N,N-di)(lower)alkylcarbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino-(lower)alkyl]carbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl]carbamoyl(lower)alkyl,
N-[amino(or protected amino)(lower)alkyl]-carbamoyl(lower)alkyl,
heterocyclic-thio(lower)alkyl optionally substituted by lower alkyl,
lower alkylthio(lower)alkyl,
di(lower)alkylsulfonio(lower)alkyl,
halo(lower)alkylthio(lower)alkyl,
lower alkoxy(lower)alkyl,
carbamoyloxy(lower)alkyl,
acylamino(lower)alkyl,
amino(or protected amino)(lower)alkyl,
lower alkylamino(lower)alkyl,
N-protected-N-(lower)alkylamino(lower)alkyl,
[carbamoyl(lower)alkylamino](lower)alkyl,
N-protected-N-[carbamoyl(lower)alkyl]amino(lower)-alkyl,
N-carbamoyl(lower)alkyl-N-(lower)alkylamino(lower) alkyl,
N-carbamoyl(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl,
N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)-alkylamino(lower)alkyl,
N-(lower alkylcarbamoyl)(lower)alkyl-N,N-di(lower)-

alkylammonio(lower)alkyl,
heterocyclic-carbonyl(lower)alkyl optionally substituted by the group consisting of hydroxy and amino(or protected amino)(lower)alkanoyl,
heterocyclic(lower)alkyl optionally substituted by the group consisting of lower alkyl and hydroxy(lower)alkyl,
heterocyclic(lower)alkenyl optionally substituted by the group consisting of lower alkyl and carbamoyl(lower)alkyl,
[hydroxy(lower)alkyl]amino(lower)alkyl,
N-protected-N-[protected hydroxy(lower)alkyl]-amino(lower)alkyl,
N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino(lower)-alkyl,
N,N-di(lower)alkyl-N-[hydroxy(lower)alkyl]ammonio-(lower)alkyl,
N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]carbamoyl-(lower)alkyl]amino(lower)alkyl,
N,N-di(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]ammonio(lower)alkyl,
N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]amino-(lower)alkyl, or
N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-ammonio(lower)alkyl, and R^5 is hydrogen, or

R^4 is hydrogen and R^5 is heterocyclic group or lower alkyl, or

R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkyliminio, or

R^4 and R^5 are combined together to form optionally substituted imino-containing heterocyclic group.

4. The compound of Claim 4, wherein

R^1 is carboxy or COO^-,

R^2 is hydroxy(lower)alkyl,

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R^3 is lower alkyl, and

R^4 is carbamoyl(lower)alkyl,
N-(or N,N-di)(lower)alkylcarbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N-(lower)alkylamino(lower)-alkyl]carbamoyl(lower)alkyl,
N-[N-hydroxy(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl]carbamoyl(lower)alkyl,
N-[amino(or lower alkenyloxycarbonylamino)(lower)-alkyl]carbamoyl(lower)alkyl,
lower alkyltetrazolylthio(lower)alkyl,
lower alkylthio(lower)alkyl,
di(lower)alkylsulfonio(lower)alkyl,
halo(lower)alkylthio(lower)alkyl,
lower alkoxy(lower)alkyl,
carbamoyloxy(lower)alkyl,
lower alkanoylamino(lower)alkyl,
halo(lower)alkanoylamino(lower)alkyl,
lower alkoxycarbonylamino(lower)alkyl,
lower alkoxy(lower)alkanoylamino(lower)alkyl,
lower alkylsulfonylamino(lower)alkyl,
carbamoylamino(lower)alkyl,
phenyl(lower)alkoxycarbonylamino(lower)alkyl,
amino[or lower alkenyloxycarbonylamino or nitro-(C_6-C_{10})ar(lower)alkoxycarbonylamino](lower)alkyl,
lower alkylamino(lower)alkyl,
N-(lower)alkenyloxycarbonyl-N-(lower)alkylamino-(lower)alkyl,
[carbamoyl(lower)alkylamino](lower)alkyl,
N-(lower)alkenyloxycarbonyl-N-[carbamoyl(lower)-alkyl]amino(lower)alkyl,
N-carbamoyl(lower)alkyl-N-(lower)alkylamino-(lower)alkyl,
N-carbamoyl(lower)alkyl-N,N-di(lower)alkylammonio-(lower)alkyl,
[N-(lower alkylcarbamoyl)(lower)alkyl-N-(lower)-

alkylamino(lower)alkyl,
N-(lower alkylcarbamoyl(lower)alkyl-N,N-di(lower)-alkylammonio(lower)alkyl,
hydroxyazetidinylcarbonyl(lower)alkyl,
amino(or lower alkenyloxycarbonylamino)(lower)-alkanoylpiperazinylcarbonyl(lower)alkyl,
pyridyl(lower)alkyl,
lower alkylpyridyl(lower)alkyl,
imidazolyl(lower)alkyl,
lower alkylimidazolyl(lower)alkyl,
hydroxy(lower)alkylimidazolyl(lower)alkyl optionally substituted by lower alkyl,
thiazolyl(lower)alkyl,
pyrazolyl(lower)alkyl,
pyrrolidinyl(lower)alkyl,
lower alkylpyrrolidinyl(lower)alkyl,
pyridyl(lower)alkenyl,
lower alkylpyridyl(lower)alkenyl,
carbamoyl(lower)alkylpyridyl(lower)alkyl,
lower alkylimidazolyl(lower)alkenyl,
[hydroxy(lower)alkyl]amino(lower)alkyl,
N-(lower)alkenyloxycarbonyl-N-[lower alkenyloxy-carbonyloxy(lower)alkyl]amino(lower)alkyl,
N-(lower)alkyl-N-[hydroxy(lower)alkyl]amino(lower)-alkyl,
N,N-di(lower)alkyl-N-[hydroxy(lower)alkyl]ammonio-(lower)alkyl,
N-(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]amino(lower)alkyl,
N,N-di(lower)alkyl-N-[N-[hydroxy(lower)alkyl]-carbamoyl(lower)alkyl]ammonio(lower)alkyl,
N-(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-amino(lower)alkyl, or
N,N-di(lower)alkyl-N-[carbamoyloxy(lower)alkyl]-ammonio(lower)alkyl, and R^5 is hydrogen, or
R^4 is hydrogen and R^5 is thiadiazolyl or lower alkyl, or

R^4 is hydrogen and the formula : $=N-R^5$ is N,N-di(lower)alkyliminio, or
R^4 and R^5 are combined together to form 1-pyrrolinyl ring optionally substituted by lower alkyl.

5. The compound of Claim 4, wherein
R^1 is carboxy or COO^-,
R^2 is 1-hydroxyethyl,
R^3 is methyl,
R^4 is carbamoylmethyl,
N,N-dimethylcarbamoylmethyl,
[N-[2-[N-(2-hydroxyethyl)-N-methylamino]ethyl]-carbamoyl]methyl,
[N-[2-[N-(2-hydroxyethyl)-N,N-dimethylammonio]-ethyl]carbamoyl]methyl,
N-(4-aminobutyl)carbamoylmethyl,
N-(4-allyloxycarbonylaminobutyl)carbamoylmethyl,
(1-methyltetrazol-5-ylthio)methyl,
methylthiomethyl,
dimethylsulfoniomethyl,
difluoromethylthiomethyl,
methoxymethyl,
carbamoyloxymethyl,
acetylaminomethyl,
trifluoroacetylaminomethyl,
methoxycarbonylaminomethyl,
methoxyacetylaminomethyl,
methylsulfonylaminomethyl,
carbamoylaminomethyl,
2-(benzyloxycarbonylamino)ethyl, aminomethyl,
2-aminoethyl, allyloxycarbonylaminomethyl,
2-(p-nitrobenzyloxycarbonylamino)ethyl,
methylaminomethyl,
(N-allyloxycarbonyl-N-methylamino)methyl,
(carbamoylmethylamino)methyl,
2-(carbamoylmethylamino)ethyl,

[N-allyloxycarbonyl-N-(carbamoylmethyl)amino]methyl,
2-[N-allyloxycarbonyl-N-(carbamoylmethyl)amino]ethyl,
2-(N-carbamoylmethyl-N-methylamino)ethyl,
3-(N-carbamoylmethyl-N,N-dimethylammonio)propyl,
3-[N-(methylcarbamoyl)methyl-N-methylamino]propyl,
3-[N-(methylcarbamoyl)methyl-N,N-dimethylammonio]-propyl,
4-hydroxyazetidin-1-ylcarbonylmethyl,
[4-(5-aminopentanoyl)piperazin-1-yl]carbonylmethyl,
[4-(5-allyloxycarbonylaminopentanoyl)piperazin-1-yl]-carbonylmethyl,
3-pyridylmethyl,
2-(3-pyridyl)ethyl,
3-(1-pyridinio)propyl,
(1-methyl-3-pyridinio)methyl,
2-(1-methyl-3-pyridinio)ethyl,
3-(1-imidazolyl)propyl,
4-imidazolylmethyl,
2-(4-imidazolyl)ethyl,
3-(2-methylimidazol-1-yl)propyl,
(3-methyl-1-imidazolio)methyl,
3-(3-methyl-1-imidazolio)propyl,
5-(3-methyl-1-imidazolio)pentyl,
1,3-dimethyl-2(or 4)-imidazoliomethyl,
3-[3-(2-hydroxyethyl)-1-imidazolio]propyl,
3-(4-hydroxymethyl-1-methyl-3-imidazolio)propyl,
3-(3-thiazolio)propyl,
(1,2-dimethyl-4-pyrazolio)methyl,
3-(1-pyrrolidinyl)propyl,
3-(1-methyl-1-pyrrolidinio)propyl,
2-(3-pyridyl)ethenyl,
2-(1-methyl-3-pyridinio)ethenyl,
2-(1-carbamoylmethyl-3-pyridinio)ethenyl,
2-(1,3-dimethyl-2-imidazolio)ethenyl,
(2-hydroxyethylamino)methyl,

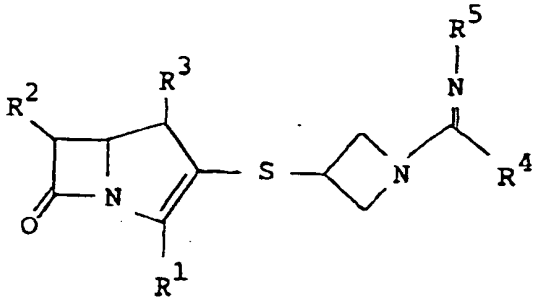
2-(2-hydroxyethylamino)ethyl, [N-allyloxycarbonyl-N-[2-(allyloxycarbonyloxy)ethyl]amino]methyl, 2-[N-methyl-N-(2-hydroxyethyl)amino]ethyl, 3-[N-methyl-N-(2-hydroxyethyl)amino]propyl, 3-[N,N-dimethyl-N-(2-hydroxyethyl)ammonio]propyl, 3-[N-methyl-N-[N-(2-hydroxyethyl)carbamoylmethyl]-amino]propyl, 3-[N-methyl-N-[N-(2-hydroxyethyl)carbamoylmethyl]-ammonio]propyl, 3-[N-methyl-N-[2-(carbamoyloxy)ethyl]amino]propyl, or 3-[N,N-dimethyl-N-[2-(carbamoyloxy)ethyl]ammonio]-propyl, and R^5 is hydrogen, or

R^4 is hydrogen and R^5 is 1,3,4-thiadiazol-5-yl, or methyl, or

R^4 is hydrogen and the formula : =N-R is N,N-dimethylimino, or

R^4 and R^5 are combined together to form 1-methyl-2-pyrrolinio ring.

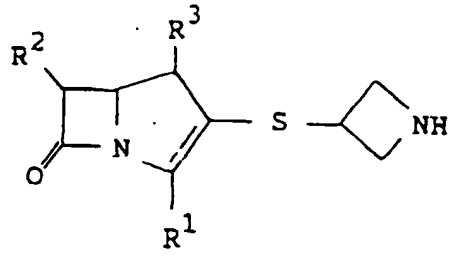
6. A process for the preparation of a compound of the formula :



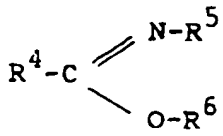
in which R^1, R^2, R^3, R^4 and R^5 are each as defined in Claim 1,

or salts thereof, which comprises

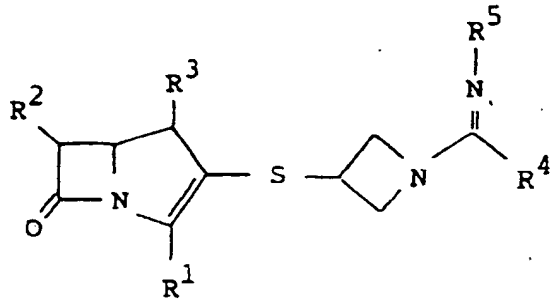
(a) reacting a compound of the formula :



wherein R^1, R^2 and R^3 are each as defined above,
or salts thereof with a compound of the formula :



wherein R^4 and R^5 are each as defined above, and
R^6 is lower alkyl,
or salts thereof to give a compound of the formula :



wherein R^1, R^2, R^3, R^4 and R^5 are each as defined above,
or salts thereof; and

(b) subjecting a compound of the formula :

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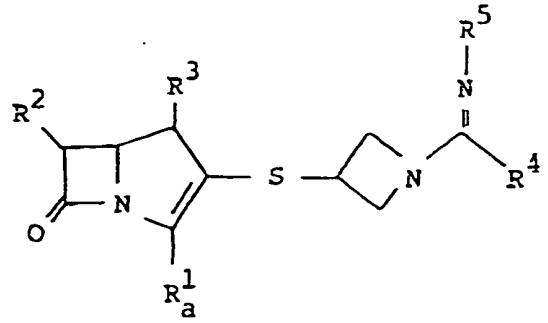
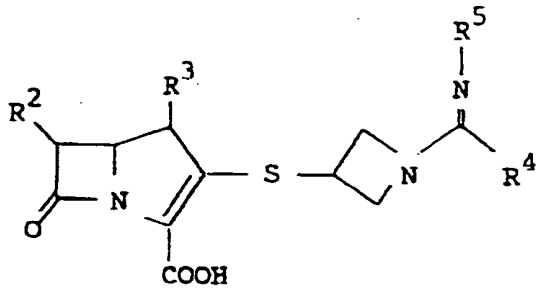
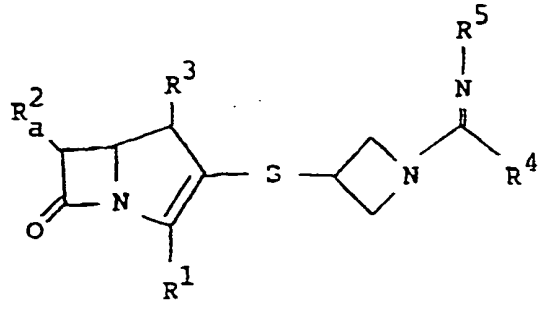


wherein R^2, R^3, R^4 and R^5 are each as defined above,
and
R_a^1 is protected carboxy,
or salts thereof to removal reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



wherein R^2, R^3, R^4 and R^5 are each as defined above, or salts thereof; and

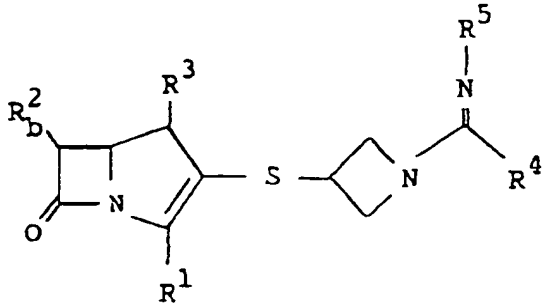
(c) subjecting a compound of the formula :



wherein R^1, R^3, R^4 and R^5 are each as defined above, and

R_a^2 is protected hydroxy(lower)alkyl,

or salts thereof to removal reaction of the hydroxy-protective group on R_a^2 to give a compound of the formula :

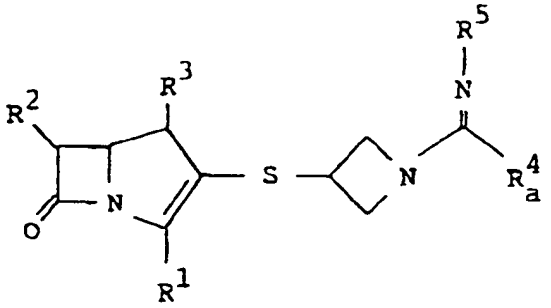


wherein R^1, R^3, R^4 and R^5 are each as defined above, and

R_b^2 is hydroxy(lower)alkyl,

or salts thereof; and

(d) subjecting a compound of the formula :



wherein R^1, R^2, R^3 and R^5 are each as defined above,

R_a^4 is substituted lower alkyl or substituted lower alkenyl containing protected amino- and/or protected hydroxy-moiety(ies), and R^5 is

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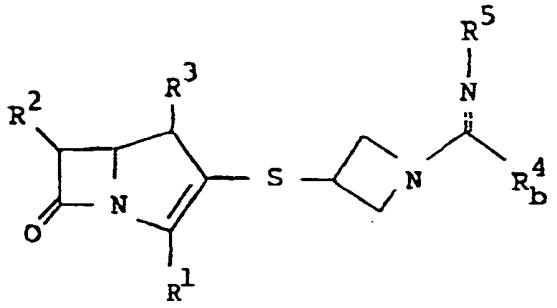
hydrogen,

or salts thereof to removal reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



wherein R^1, R^2, R^3 and R^5 are each as defined above, and

R_b^4 is substituted lower alkyl or substituted lower alkenyl containing amino- and/or hydroxy-moiety(ies), and R^5 is hydrogen,

or salts thereof.

7. A pharmaceutical composition comprising, as an active ingredient, a compound of Claim 1, in admixture with a pharmaceutically acceptable carrier or excipient.

8. Use of a compound of Claim 1 as an antimicrobial agent.

9. Use of a compound of Claim 1 for the manufacture of a medicament for therapeutic treatment of infectious diseases to human being or animal.

10. A method for the treatment of infectious diseases with comprises administering a compound of Claim 1 to human being or animal.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 93/00598

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D477/00; A61K31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	EP,A,0 394 991 (FUJISAWA PHARMACEUTICAL CO. , LTD.) 31 October 1990 see examples 19-3, 27-16, 32-1-2-3 and claims	1-10
Y	WO,A,9 202 521 (FUJISAWA PHARMACEUTICAL CO. , LTD.) 20 February 1992 see pages 136-137, example 8-5 and claims	1-10
Y	EP,A,0 186 525 (SANKYO COMPANY LTD.) 2 July 1986 see claims	1-10
Y	EP,A,0 072 710 (SANKYO COMPANY LTD.) 23 February 1983 see claims; examples 3,8,19	1-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 JUNE 1993	- 8. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	CHOULY J.

Form PCT/ISA/210 (second sheet) (January 1985)

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INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/JP 93/00598

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9300598
SA 73523

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0394991	31-10-90	JP-A-	2300187	12-12-90
		US-A-	5102877	07-04-92
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		GB-A,B	2104075	02-03-83
		GB-A,B	2121792	04-01-84
		GB-A,B	2163156	19-02-86
		US-A-	4552873	12-11-85
		US-A-	4613595	23-09-86

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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